

Primary Care of
Veterans with HIV



Primary Care of Veterans with HIV

HIV, Hepatitis and Related Conditions Programs (HHRC)
in the Office of Specialty Care Services
Veterans Health Administration
U.S. Department of Veterans Affairs

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IMPORTANT NOTICE

The editors of this manual are committed to providing accurate information on HIV-related care. However, please be aware that therapy options and protocols continue to change. Readers are invited to check for updates to drug information at Drugs@FDA (<http://www.accessdata.fda.gov/scripts/cder/drugsatfda/>) and to treatment guidelines at AIDS Info (<http://aidsinfo.nih.gov/>).

We hope that you will send feedback and suggestions for future editions to: VHAHRC@va.gov

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Introduction

In 2009, the first edition of *Primary Care of Veterans with HIV* was released, quickly becoming an important resource for providers delivering high-quality primary care to Veterans living with HIV. Over the past decade, as more Veterans with HIV infection in care in facilities operated by the U.S. Department of Veterans Affairs (VA) have been diagnosed, linked to care, and started on highly active antiretroviral therapy (HAART), the role of primary care has grown, with much of this care provided not only through HIV specialty care clinics but also via Infectious Disease-Patient Aligned Care Teams. Much of this is provided not only through HIV specialty care clinics but also via infectious Disease-Patient Aligned Care Teams. The phenomenal benefits of HAART are perhaps best illustrated by survival of these Veterans into their eighth decade of life. Over the last decade, the proportion of Veterans in VA care with HIV aged 70 years and up has increased from 5% to 15%. The aging of this population has made management of conditions traditionally associated with other individuals, such as cardiovascular disease, diabetes, and malignancy, even more important.

Recognizing a continued need to focus on age-related comorbid illnesses, substance use, and other critical issues for Veterans living with HIV, we have updated and added to this original resource. This manual serves as a point-of-care reference for HIV clinicians providing HIV and primary care to their HIV patients. We hope it will also be of use to non-VA providers who care for Veterans with HIV outside of the VA healthcare system. This manual is meant to be a practical guide to screening and treatment of many of the most common and serious comorbid conditions among people living with HIV.

The HIV, Hepatitis, and Related Conditions Programs in the VA Office of Specialty Care Services would like to thank all the VA subject matter experts who contributed to the update of this manual. We gratefully acknowledge their expertise, enthusiasm, and the countless hours they dedicated to revising a resource aimed at improving the care and well-being of our Veterans. We also extend our thanks to members of the VA HIV Technical Advisory Group for their advice and guidance.

Comments and suggestions regarding this manual are welcome, and can be e-mailed to hivhhrc@va.gov.

This manual is dedicated to all the providers across the VA system who strive to provide excellent HIV care to our Veterans, and to the Veterans who have entrusted the VA with their care.

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Abbreviations for Antiretroviral Drugs and Dosing Instructions Commonly Used in This Manual

DOSING TERMINOLOGY

BID = twice daily
IM = intramuscular
IV = intravenous
PO = orally
PRN = as needed
Q2H, Q4H, etc = every 2 hours,
every 4 hours, etc
QAM = every morning
QD = once daily
QH = every hour
QHS = every night at bedtime
QID = 4 times per day
QOD = every other day
TID = 3 times per day
TIW = 3 times per week

ANTIRETROVIRAL TERMINOLOGY

ART = antiretroviral therapy
ARV = antiretroviral
FI = fusion inhibitor
NNRTI = nonnucleoside
reverse transcriptase inhibitor
NRTI = nucleoside (or nucleotide)
reverse transcriptase inhibitor
PI = protease inhibitor

ANTIRETROVIRAL DRUGS

3TC = lamivudine
ABC = abacavir
APV = amprenavir
ATV = atazanavir
d4T = stavudine
ddC = zalcitabine
ddl = didanosine
DLV = delavirdine
DRV = darunavir
EFV = efavirenz
ENF = enfuvirtide
ETR = etravirine
FPV = fosamprenavir
FTC = emtricitabine
IDV = indinavir
LPV/r = lopinavir/ritonavir
MVC = maraviroc
NFV = nelfinavir
NVP = nevirapine
RAL = raltegravir
RTV = ritonavir
/r = ritonavir, low dose
SQV = saquinavir
TDF = tenofovir
TPV = tipranavir
ZDV = zidovudine

Caring for a Veteran with HIV

Caring for a Veteran with HIV

Wide availability of antiretroviral (ARV) therapy regimens enables most patients infected with Human Immunodeficiency Virus (HIV) to enjoy the same life expectancy as the general population. ARV therapy is now recommended for all patients who are HIV-infected, regardless of their CD4 cell count, to reduce mortality, morbidity and transmission rate. Upon starting ARV therapy, it is important to educate patients about benefits and side effects, and address strategies to increase adherence.

One in 96 Americans will be diagnosed with HIV in their lifetime. The male population has a higher estimated lifetime risk than the female population. Exact statistics in the Veteran population has not yet been studied.

ARV therapy side effects and drug interactions are numerous and complex. Within the infected population, the primary care clinician is the first line of defense against poor adherence to the treatment and aggravated side effects. See **Comorbid Conditions**, p. 313, for more information about side effects.

Impact on Patient Population

Two main routes of contracting HIV are having unprotected sex, especially in men who have sex with men (MSM) population, and IV drug use. Veterans may be especially unwilling to acknowledge these underlying behaviors. Veterans with an HIV-positive test can be stigmatized by their peers and perceived to have participated in these activities. This situation can lead to desperation and alienation. It is important to discern the signs of pariah status and provide necessary support to the impacted patients.

There are a few unique issues for the Veteran patient described here. Throughout the manual, we will primarily use “patient.” However, when there are issues specific to the Veteran population, we will use the term “Veteran”.

Dealing with a Positive HIV Test

Patients who are HIV positive are at high risk of suffering mental health issues throughout the progression of the disease. Specific episodes can instigate major mental health challenges for patients. These events include but are not limited to the positive HIV test, the initial onset of physical symptoms, sudden decline in the CD4 count, the first opportunistic infection and the first hospitalization. Depression, anxiety and stress are common among older patients who are HIV-positive. Psychological support for patients with HIV and their partners or family member is an important aspect of holistic HIV management. Counseling for patients with HIV is crucial to understand the patient needs and refer them to the relevant specialists, including psychologists, social workers or dietitians. Studies suggest a canine companion is an effective treatment to improve the mental well-being of patients with HIV.

Patients with HIV may also suffer from economic hardship and social isolation. Moreover, patients who are HIV-positive with minority racial/ethnic identity, minority sexual preference, low socioeconomic status and intergenerational poverty, and limited social supports report increased challenges in dealing with an HIV diagnosis.

It is important for the primary care physician to establish that the patients who contract the disease can live fulfilling lives and with the advent of the ARV therapy drug regimens, there is minimal impact on the daily activities of patients. Patients experiencing withdrawal from social activities because of the stigma of HIV need to be reassured that social activities may be resumed.

Stigma and Discrimination

High clinical suspicion of disease and regular testing for HIV is helpful for both patients and society by improving treatment and decreasing transmission rate in this contagious period of infection. Primary care clinicians are tasked to overcome two significant psychological barriers. Clinicians need to gain acceptance from the patient for the necessary HIV test and at the same time they need to ensure that the patients with positive HIV tests understand that a full life can be lived with ARV therapy regimens.

Frequency of Clinical Evaluation

Frequent visits may be appropriate for new patients and patients who have recently started ARV therapy. Side effects of ARV therapy and possible drug interactions will provide significant challenges in the starting phase of the treatment. Once the viral load has been suppressed and CD4 cell count is increased and stable less frequent monitoring is appropriate. Follow the U.S. Department of Health and Human Services guidelines for ARV therapy.

Necessary Tests

According to the Department of Health and Human Services (DHHS) HIV treatment guidelines and HIV Medicine Association the laboratory tests listed below are beneficial in caring for patients with HIV infection.

- CD4 count – needs to be checked at the initiation of the care and then every 3-6 months or even yearly, depending on situation.
- HIV viral load – needs to be measured at the beginning of the care and every 3-4 months; however, it can be extended to every 6 months in some situations.
- CBC, electrolyte panel, liver enzymes, bilirubin level, lipid panel, HIV genotype, and urinalysis – All patients who receive a diagnosis of HIV require screening for other sexually transmitted infections, including chlamydia, gonorrhea, and syphilis. Screening for tuberculosis and serologies for toxoplasma and viral hepatitis are also indicated.

- All women need a cervical papanicolaou test, and premenopausal women should have a pregnancy test. In a patient with concerning symptoms of hypogonadism, measuring morning serum total testosterone can be helpful.

Immunization

Preventing patients who are HIV-infected from contracting vaccine-preventable illnesses is an important part of primary care. These vaccines are recommended:

- H influenza type B vaccine – for asplenic patients and those with history of recurrent haemophilus infection
- Hepatitis A vaccine – for susceptible MSM and those with an indication for hepatitis A vaccine
- Hepatitis B vaccine – administer to patients without evidence of past or present hepatitis B infection
- Human papillomavirus (HPV) vaccine – administer to all aged 13-26 years if not previously vaccinated
- Influenza vaccine – annually. Inactivated vaccine is recommended
- Pneumococcal vaccine – it is necessary for all patients with CD4 >200
- Polio – Inactivated polio vaccine should be given only if indicated
- Tetanus toxoid – same indication as patients without HIV
- MMR – administer to all nonimmune persons with CD4 counts of 200 or more
- Varicella zoster vaccine (VZV) – consider for HIV-infected, VZV-seronegative patients with CD4 counts of 200 or more
- Meningococcal conjugate vaccine – for persons aged 2 months or older with HIV infection

Drug-Drug Interaction

Cytochrome P450 system metabolizes multiple HIV medications in the non-nucleoside reverse transcriptase inhibitor and protease inhibitor classes. Possible drug interactions should be reviewed before administering new medication. Complications with HIV treatment and comorbidities present in patients with HIV leads to common prescriptions for cytochrome P450 metabolized drugs including benzodiazepines; cholesterol-lowering, anti-seizure, erectile dysfunction agents, and warfarin. Additionally, herbal supplements such as St John's wort and garlic supplements have demonstrated adverse interaction with HIV medication.

Monitoring for Complications

Since the start of ARV therapy, mortality of patients with HIV has decreased and comorbidities have increased and develop at a younger age than in the general population.

These complications include metabolic complication and some malignancies. As a result, primary care clinicians have an active role in the management of patients with HIV. Primary care clinicians with knowledge about prevention and management of chronic diseases can be utilized to manage care for patients with an HIV-positive diagnosis that exhibit chronic illness as they age.

Other

Counselling for behavioral risk reduction is an essential part of HIV care. At each visit, the practitioner should review the patient's knowledge of HIV transmission and his/her sexual and drug-use activities. Patients who are HIV-infected should avoid eating high bacterial load food items, including raw eggs, unpasteurized dairy products, raw seafood and undercooked meat. They should not drink water from untested sources. Other relevant counselling issues for patients who are HIV-infected may include pet and travel safety.

Primary care providers (PCPs) are the first line in managing patients infected with HIV for chronic illness, psychological issues and drug complications. It is imperative that the necessary resources are provided to ensure best practices. The relevant topics will be discussed with further details in the following chapters.



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Interactions Tables

Common Medications: ARV Interactions

For information on potential ARV interactions with the following medications, see the specified chapters:

Acid-lowering medications (See **Gastroesophageal Reflux Disease (GERD)**, p. 431)

Hormonal contraceptives (See **Women's Health**, p. 283)

Lipid-lowering medications (See **Lipid-Lowering Medications**, p. 25)

Psychoactive medications: antidepressants, sedatives, antipsychotics (See **Psychoactive Medications**, p. 41)

St. John's wort (See **Food and Supplements**, p. 23)

Antiepileptic Medications

Carbamazepine, phenytoin, and phenobarbital may ↓ PI and NNRTI levels substantially.

Medication	ARV Interactions	Comments
Carbamazepine CYP450 inducer	PIs: may ↓ PI levels <ul style="list-style-type: none"> • ATV: ↑ carbamazepine levels • DRV: ↑ carbamazepine AUC 45% • RTV: ↑ carbamazepine levels • LPV/r: ↑ carbamazepine levels • Other PIs: may also ↑ carbamazepine levels • COBI: ↓ COBI levels 	Should not be used; use alternative antiepileptics. <ul style="list-style-type: none"> • Contraindicated with ATV/c or DRV/c DRV: no significant change DRV/r: Monitor anticonvulsant level and adjust dose accordingly. ATV/r, LPV/r: Consider alternative anticonvulsant or monitor levels of both drugs and assess virologic response. Do not coadminister with LPV/r QDay. <p>Two-way interactions also affect PI and NNRTI levels.</p>
	NNRTIs: may ↓ levels of all NNRTIs <ul style="list-style-type: none"> • EFV: ↓ carbamazepine AUC 27%; ↓ EFV levels 	Monitor carbamazepine and EFV/NVP levels, if possible; use alternative antiepileptics. ETR and RPV should not

Note: Some medications mentioned in this chapter may not be available on the VHA National Formulary (<https://www.pbm.va.gov/NationalFormulary.asp>). Consult VA pharmacists for alternatives.

Medication	ARV Interactions	Comments
-	36% <ul style="list-style-type: none"> • ETR and NVP: ↓ carbamazepine and NNRTI levels • RPV: expect ↓ RPV levels 	be coadministered.
	NRTIs TAF: ↓ TAF possible	Consider alternative anticonvulsant.
	INSTIs <ul style="list-style-type: none"> • DTG: ↓ DTG levels possible • EVG/c: carbamazepine AUC ↑ 43% EVG AUC ↓ 69% and C_{min} ↓ >99% ↓ COBI expected • EVG plus PI/r: ↓ EVG 	DTG: Consider alternative anticonvulsant. EVG/c: Contraindicated. Do not coadminister. EVG plus PI/r: Consider alternative anticonvulsant.
	MVC: ↓ MVC levels	If used concurrently without a strong CYP 3A4 inhibitor, give MVC 600 mg BID or alternative antiepileptic agent.
Phenobarbital CYP450 inducer	PIs: may ↓ PI levels <ul style="list-style-type: none"> • DRV: ↓ phenobarbital levels • RTV: ↓ phenobarbital levels • COBI: ↓ COBI levels 	Should not be used; use alternative antiepileptics. <ul style="list-style-type: none"> • Contraindicated with ATV/c or DRV/c. Avoid concomitant use if possible; use alternative antiepileptics. Do not coadminister with LPV/r once daily or unboosted ATV. Two-way interactions also affect PI and NNRTI levels.
	NNRTIs: may ↓ NNRTI levels <ul style="list-style-type: none"> • EFV and NVP: ↓ phenobarbital levels • ETR: ↓ ETR levels • RPV: expect ↓ RPV levels 	Monitor phenobarbital and EFV/NVP levels, if possible; use alternative antiepileptics. ETR and RPV should not be coadministered.
	NRTIs TAF: ↓ TAF possible	Consider alternative anticonvulsant.

Medication	ARV Interactions	Comments
-	<p>INSTIs</p> <ul style="list-style-type: none"> DTG: ↓ DTG levels possible <p>EVG/c: carbamazepine AUC ↑ 43% EVG AUC ↓ 69% and C_{min} ↓ >99% ↓ COBI expected</p> <p>EVG plus PI/r: ↓ EVG</p>	<p>DTG: Consider alternative anticonvulsant.</p> <p>EVG/c: Contraindicated. Do not coadminister.</p> <p>EVG plus PI/r: Consider alternative anticonvulsant.</p>
<p>Phenytoin CYP450 inducer</p>	<p>PIs: may ↓ PI levels</p> <ul style="list-style-type: none"> DRV: ↓ phenytoin levels ATV: ↓ phenytoin levels LPV/r: ↓ LPV/r AUC 33%, ↓ ↓ phenytoin AUC 31% RTV: anticipate ↓ phenytoin levels COBI: ↓ COBI levels 	<p>Contraindicated with COBI</p> <p>Avoid if possible; use alternative antiepileptics.</p> <p>Two-way interactions also affect PI and NNRTI levels.</p> <p>Do not co-administer with ATV, LPV/r QDay.</p>
	<p>NNRTIs: may ↓ NNRTI levels</p> <ul style="list-style-type: none"> EFV: ↓ phenytoin levels, ↓ EFV levels ETR: ↓ ETR and phenytoin levels NVP: ↓ phenytoin and NVP levels RPV: ↓ RPV expected 	<p>Monitor phenytoin and EFV/NVP levels, if possible; use alternative antiepileptics.</p> <p>ETR and RPV should not be coadministered.</p>
	<p>NRTIs</p> <p>TAF: ↓ TAF possible</p> <p>INSTIs</p> <ul style="list-style-type: none"> DTG: ↓ DTG levels possible <p>EVG/c: carbamazepine AUC ↑ 43% EVG AUC ↓ 69%</p>	<p>Consider alternative anticonvulsant.</p> <p>DTG: Consider alternative anticonvulsant.</p> <p>EVG/c: Contraindicated. Do not coadminister.</p> <p>EVG plus PI/r: Consider alternative anticonvulsant.</p>

Medication	ARV Interactions	Comments
-	and C_{min} ↓ >99% ↓ COBI expected EVG plus PI/r: ↓ EVG	-
	MVC: ↓ MVC levels	If used concurrently without a strong CYP 3A4 inhibitor, give MVC 600 mg BID or alternative antiepileptic agent.
Valproate	PIs	Monitor VPA levels and virologic response. Monitor for LPV-related toxicities.
	<ul style="list-style-type: none"> LPV /r: ↑ LPV AUC 75%, may ↓ valproate levels 	
	NNRTIs: no significant changes in NNRTI or valproate levels	-
Lamotrigine	PIs	Dose increase of lamotrigine may be needed; consider TDM or an alternative. No data when used with COBI.
	<ul style="list-style-type: none"> ATV/r: ↓ lamotrigine levels 32% LPV/r: ↓ lamotrigine levels 50% RTV: ↓ lamotrigine levels 	

Antifungal Medications

Medication	ARV Interactions	Comments
Fluconazole Inhibitor of CYP 2C9	PIs	No dosage adjustment necessary.
	<ul style="list-style-type: none"> ATV/r or ATV/c: no significant change 	
	NNRTIs	Avoid use with NVP. EFV, ETR: dosage adjustment not required. RPV: no dose adjustment needed. Monitor for breakthrough fungal infection.
	<ul style="list-style-type: none"> NVP: 110% ↑ in NVP levels EFV: no significant change ETR, RPV: potential ↑ in NNRTI levels 	

Medication	ARV Interactions	Comments
Isavuconazole	PIs <ul style="list-style-type: none"> • LPV/r: ↑ isavuconazole AUC 96%; ↓ LPV/r AUC 27% • All other PIs: ↑ isavuconazole possible; variable effect on PI 	If coadministered, consider monitoring isavuconazole concentrations. Monitor for PI toxicity and virologic response.
	NNRTIs <ul style="list-style-type: none"> • EFV, ETR, NVP: ↓ isavuconazole possible • RPV: ↓ possible but lesser extent; ↑ RPV possible 	Dose adjustments for isavuconazole may be necessary with EFV, ETR, NVP. Consider monitoring levels and antifungal response. No dose adjustment necessary. Monitor for breakthrough fungal infection.
	INSTIs <ul style="list-style-type: none"> • EVG/c: ↑ isavuconazole expected; ↑ EVG and COBI possible • EVG plus PI/r: Changes in isavuconazole and EVG possible 	If coadministered, consider monitoring isavuconazole concentrations. Monitor for PI toxicity and virologic response.
	MVC: ↑ MVC levels	Consider dose reduction to MVC 150mg BID.
Itraconazole Inhibitor and substrate of CYP 3A4	PIs: ↑ PI levels and ↑ itraconazole levels	Consider monitoring itraconazole levels. Avoid itraconazole dosages >200 mg daily with patients who take PIs.
	NNRTIs <ul style="list-style-type: none"> • EFV: ↓ itraconazole levels and its metabolite by 35 to 44% • ETR: ↓ itraconazole levels and ↑ ETR • NVP: ↓ itraconazole levels and ↑ NVP 	Failure to achieve therapeutic itraconazole concentrations has been reported with EFV. Avoid combination with EFV, NVP if possible. If used concomitantly, monitor itra levels. Dose adjustments for itra may be necessary with ETR. Monitor itra levels and antifungal response.

Medication	ARV Interactions	Comments
-	<ul style="list-style-type: none"> RPV: ↓ itraconazole levels and ↑ RPV 	No dose adjustment necessary with RPV. Monitor for breakthrough fungal infection.
	<p>INSTIs</p> <ul style="list-style-type: none"> EVG/c: ↑ itraconazole expected; ↑ EVG and COBI possible EVG plus PI/r: ↑ EVG possible 	Consider monitoring itraconazole levels. Avoid itraconazole dosages >200 mg daily with patients who take PIs, unless dose is guided by itraconazole levels.
	MVC: ↑ MVC levels	MVC 150 mg BID
Posaconazole Inhibitor of CYP 3A4	<p>PIs</p> <ul style="list-style-type: none"> RTV: ↑ RTV levels ATV: ↑ ATV levels Other PIs: ↑ PI and posaconazole levels 	If coadministered, monitor posaconazole levels. Monitor laboratory values frequently for signs of toxicity.
	<p>NNRTIs</p> <ul style="list-style-type: none"> EFV: ↓ posaconazole levels by 50% TR: ↑ ETR levels RPV: ↓ posaconazole possible. ↑ RPV possible 	Avoid concomitant use with EFV unless benefit outweighs risk. If needed, monitor posaconazole concentration and adjust dose accordingly. No dose adjustment necessary with ETR or RPV. Monitor for breakthrough fungal infection.
	MVC: ↑ MVC levels	MVC 150 mg BID
	<p>INSTIs</p> <ul style="list-style-type: none"> EVG/c: ↑ posaconazole possible; ↑ EVG and COBI possible EVG plus PI/r: ↑ EVG possible 	If coadministered, monitor posaconazole levels. Monitor laboratory values frequently for signs of toxicity.
Terbinafine: Inhibitor of CYP 2D6	PIs: no significant changes	No dosage adjustments necessary.
	NNRTIs: no significant changes	No dosage adjustments necessary.

Medication	ARV Interactions	Comments
Voriconazole CYP 3A4, CYP 2C9, and CYP 2C19 inhibitor; CYP 2C19 substrate	PIs: limited data <ul style="list-style-type: none"> • COBI: Effects unknown • All PIs with RTV: voriconazole AUC ↓ 39% with RTV 100 mg BID 	Do not coadminister voriconazole with RTV or COBI unless benefit outweighs the risk. If coadministered, consider monitoring voriconazole concentration and adjust accordingly.
	NNRTIs <ul style="list-style-type: none"> • EFV: ↓ voriconazole by 77% and ↑ EFV by 44%; similar effect expected for NVP • ETR: ↑ voriconazole by 14% and ↑ ETR AUC by 36% • RPV and NVP: ↓ voriconazole possible and ↑ RPV and NVP possible 	EFV: Contraindicated at standard dosages; use voriconazole 400 mg BID and EFV 300 mg QD. ETR: dosage adjustments not established; monitor voriconazole level. NVP: Monitor for toxicity and antifungal response/ vori level. RPV: No dose adjustment necessary. Monitor for breakthrough fungal infection.
	INSTIs <ul style="list-style-type: none"> • EVG/c: ↑ voriconazole expected; ↑ EVG and COBI possible • EVG plus PI/r: Changes in voriconazole and EVG possible 	Risk/benefit ratio should be assessed to justify use of voriconazole. If coadministered, consider monitoring voriconazole concentration and adjust accordingly.
	MVC: anticipated ↑ MVC levels	Consider dose reduction to MVC 150 mg BID.
Amiodarone	PIs All PIs: ↑ both amiodarone and PI possible	Use with caution. Monitor for amiodarone toxicity and consider ECG and amiodarone drug level monitoring.
	NNRTIs All NNRTIs: amiodarone levels may be decreased	Monitor for efficacy.
	INSTIs <ul style="list-style-type: none"> • EVG/c or EVG plus PI/r: ↑ amio possible 	Use amio with caution.

Medication	ARV Interactions	Comments
Digoxin	PIs <ul style="list-style-type: none"> • PI/r, ATV/c, or DRV/c: RTV (200mg BID) ↑ digoxin AUC by 29% and ↑ half-life 43% • DRV/r: ↑ digoxin AUC 36% • COBI: ↑ digoxin C_{max} 41%; no change in AUC 	Use with caution. Monitor digoxin levels. Digoxin dose may need to be decreased. Titrate initial digoxin dose.
	NNRTIs <ul style="list-style-type: none"> • ETR: ↑ digoxin C_{max} 19% and AUC 18% 	
	INSTIs <ul style="list-style-type: none"> • EVG/c: ↑ digoxin C_{max} by 41% and AUC no significant change • EVG plus PI/r: ↑ digoxin possible 	Use digoxin with caution. Therapeutic drug monitoring is recommended.

Calcium Channel Blockers (CCBs)

Medication	ARV Interactions	Comments
Amlodipine	PIs <ul style="list-style-type: none"> • ↑ amlodipine levels 	Use with caution. Titrate CCB dose and monitor closely. ECG monitoring is recommended when used with ATV.
	INSTIs <ul style="list-style-type: none"> • EVG/c or EVG plus PI/r: ↑ amlodipine possible 	
Diltiazem	<ul style="list-style-type: none"> • ATV: ↑ diltiazem AUC 125% larger increase when boosted • All other PIs: ↑ diltiazem levels 	Decrease dose by 50% when coadministered with ATV. ECG monitoring is recommended. Use with caution. Adjust diltiazem according to clinical response and toxicities.

	NNRTIs Other NNRTIs: ↓ Diltiazem possible EFV: ↓ Diltiazem AUC 69%	Titrate diltiazem dose based on clinic response.
	INSTIs • EVG/c or EVG plus PI/r: ↑ diltiazem possible	Coadminister with caution. Titrate diltiazem dose and monitor for efficacy and toxicity.

Metadone

Medication	ARV Interactions	Comments
-	PIs • ATV/r and DRV/r: ↓ • methadone R-methadone AUC 16 to 18%, • LPV/r: ↓ methadone AUC 26 to 53% • ATV/c and DRV/c: no data	Opioid withdrawal unlikely but may occur. Dosage adjustment usually not required. Monitor for opioid withdrawal and increase methadone as indicated.
	NNRTIs • EFV: ↓ methadone AUC 52% • ETR: no change in methadone levels anticipated • NVP: ↓ methadone AUC 37 to 51% • RPV: ↓ R-methadone AUC 16%	EFV, NVP: Opioid withdrawal common; increased methadone dose often necessary. ETR: No dose adjustment necessary. RPV: No dose adjustment necessary, but monitor for withdrawal symptoms.
	INSTIs • DTG: no significant effect • EVG/c: no significant effect • EVG plus PI/r: ↓ methadone • RAL: no significant effect	No dosage adjustment with DTG, RAL, or EVG/c. EVG plus PI/r: Opioid withdrawal unlikely but may occur. Dosage adjustment usually not required. Monitor for opioid withdrawal and increase methadone as indicated.

Warfarin

Medication	ARV Interactions	Comments
-	<p>PIs</p> <ul style="list-style-type: none"> PI/r: ↓ warfarin possible ATV/c and DRV/c: No data 	<p>Start at low dosage; monitor INR closely. Adjust warfarin dosage as indicated.</p> <p>If switching between RTV and COBI the effect of COBI on warfarin is not expected to be equivalent to RTV's effect on warfarin.</p>
	<p>NNRTIs</p> <ul style="list-style-type: none"> EFV or NVP: warfarin levels may ↑ or ↓ ETR: ↑ warfarin levels (anticipated) RPV: not studied 	<p>Monitor INR closely, adjust dosage as indicated.</p>
	<p>INSTIs</p> <p>EVG/c or EVG plus PI/r: Warfarin levels may be affected</p>	<p>Monitor INR and adjust warfarin dose accordingly.</p>
Apixiban	<p>PIs</p> <p>All PIs: ↑ apixiban expected</p>	<p>Avoid concomitant use.</p>
	<p>INSTIs</p> <p>EVG/c or EVG plus PI/r: ↑ apixiban expected</p>	<p>Avoid concomitant use.</p>
Dabigatran	<p>PIs</p> <p>All PI/r, ATV/c, or DRV/c: ↑ dabigatran possible</p>	<p>No dosage adjustment for dabigatran if CrCl >50mL/min. Avoid coadministration if CrCl <50mL/min.</p>
	<p>INSTIs</p> <p>EVG/c or EVG plus PI/r: ↑ dabigatran possible</p>	<p>No dosage adjustment for dabigatran if CrCl >50mL/min. Avoid coadministration if CrCl <50mL/min.</p>

Medication	ARV Interactions	Comments
Edoxaban	PIs All PIs: ↑ edoxaban	Avoid concomitant use.
	INSTIs EVG/c or EVG plus PI/r: ↑ edoxaban expected	Avoid concomitant use.
Rivaroxaban	PIs All PIs: ↑ rivaroxaban	Avoid concomitant use.
	INSTIs EVG/c or EVG plus PI/r: ↑ rivaroxaban expected	Avoid concomitant use.
Ticagrelor	PIs All PIs: ↑ ticagrelor expected	Avoid concomitant use.
	INSTIs EVG/c or EVG plus PI/r: ↑ ticagrelor expected	Avoid concomitant use.
Vorapaxar	PIs All PIs: ↑ vorapaxar expected	Avoid concomitant use.
	INSTIs EVG/c or EVG plus PI/r: ↑ vorapaxar expected	Avoid concomitant use.
Clopidogrel	NNRTIs ETR or EFV: Possibly decreased clopidogrel effects	ETR and/or EFV may prevent metabolism of clopidogrel (inactive) to its active metabolite. Avoid combination; consider alternative agents.



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Also see product labeling for the individual ARVs.

Food and Supplements: ARV Interactions

ARVs: Food Requirements

ARV Class	No Food Restrictions	Take with Food	Take on Empty Stomach
NRTI	3TC ABC FTC TDF TAF ZDV	-	-
NNRTI	NVP	<ul style="list-style-type: none"> • ETR: take after a meal • RPV: take with a full meal 	<ul style="list-style-type: none"> • EFV: fat increases absorption and may increase the risk of EFV adverse effects. • RPV: gastric acid required for absorption; in addition, RPV levels significantly decreased if not taken with full meal.
PI	LPV/r (tablets)	ATV DRV NFV RTV TPV	-
Integrase Inhibitor	RAL DTG: if given with Ca, Fe, or MVI (see below)	EVG: take with food	-
Entry Inhibitor	ENF MVC	-	-

Note: Some medications mentioned in this chapter may not be available on the VHA National Formulary (<https://www.pbm.va.gov/NationalFormulary.asp>). Consult VA pharmacists for alternatives.

ARV Class	No Food Restrictions	Take with Food	Take on Empty Stomach
Co-formulated	Abacavir/lamivudine Abacavir/lamivudine/dolutegravir emtricitabine/tenofovir alafenamide emtricitabine/tenofovir disoproxil fumarate lamivudine/zidovudine lamivudine/zidovudine/abacavir	Emtricitabine/ripilvirine/tenofovir disoproxil emtricitabine/ripilvirine/tenofovir alafenamide emtricitabine/elvitegravir/COBI/tenofovir alafenamide emtricitabine/elvitegravir/COBI-/tenofovir disoproxil	Emtricitabine/efavirenz /tenofovir disoproxil

ARV Interactions with Specific Foods, Nutritionals, Herbs

Calcium (other divalent cations): May interfere with activity of integrase.

Separate dosing by 2 hours before or 6 hours after polyvalent cations (Mg, Al, Fe, Ca, Zn, including multivitamins with minerals). Recommended to administer DTG with calcium or iron supplements together with food.

Ginkgo Biloba: ↑ RAL AUC 21% and C_{max} 44% - no dose adjustment necessary.

St. John's wort: ↓ levels of all INSTIs, NNRTIs, and PIs. Avoid!

↓ levels of MVC; coadministration is not recommended.

Vitamin E: ↑ risk of bleeding associated with TPV. Avoid.

Echinacea, ginseng, milk thistle, vitamin C: no interactions

This information may be subject to change and for the most updated references, please consult online resources.



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Also see product labeling for the individual ARVs.

Lipid-Lowering Medications

PIs and NNRTIs can affect hepatic metabolism of HMG-coenzyme A reductase inhibitors (statins). ARVs do not generally affect the metabolism of other classes of lipid-lowering agents.

PIs	NNRTIs
<p>Most PIs inhibit the metabolism of most statins and can significantly increase serum statin levels, thus increasing the risk of toxicity, including myopathy and rhabdomyolysis.</p>	<p>NNRTI effects vary according to specific NNRTI.</p>
<p>The degree to which statin metabolism is affected by PIs varies according to the statin as well as the specific PI.</p>	<p>EFV generally induces statin metabolism, resulting in lower serum statin levels.</p>
<p>In general, the potential for inhibition of statin metabolism is as follows: simvastatin and lovastatin > atorvastatin >> fluvastatin, pravastatin, rosuvastatin >>> pitavastatin.</p>	<p>NVP has not been studied well in combination with statins, but its interactions with statins would be expected to be similar to those of EFV.</p>
<p>Fluvastatin and pitavastatin have few recognized interactions with PIs.</p>	<p>ETR has not been studied thoroughly in combination with statins. Its interactions are expected to depend on the specific statin.</p>

Medical providers should consult with a clinical pharmacist or review published information on drug interactions before prescribing statins for patients taking PIs or NNRTIs, as dosage adjustments are frequently required and some combinations are contraindicated.

Other classes of ARVs (NRTIs, fusion inhibitors, chemokine co-receptor antagonists, and integrase inhibitors) do not have recognized interactions with statins. Other types of lipid-lowering medications are not metabolized by hepatic cytochrome P450 and are not affected by ARVs.

Statins

These charts are intended for quick reference regarding drug-drug interactions. Please see the chapter on **Dyslipidemia**, (p. 417) for guideline recommendations on which agent to use.

Note: Some medications mentioned in this chapter may not be available on the VHA National Formulary (<https://www.pbm.va.gov/NationalFormulary.asp>). Consult VA pharmacists for alternatives.

Lipid-Lowering Medication	Considerations
Atorvastatin	<ul style="list-style-type: none"> • Hepatic metabolism including CYP 3A4 metabolism; extensively metabolized through hydroxylation and beta-oxidation. • PIs: significant ↑ in atorvastatin levels with most PIs (C_{max} ↑ 100-300%). • Start with lowest dosage (10 mg). Monitor antilipid activity and titrate the statin dosage cautiously. • Do not exceed 20mg daily with DRV/r. • EFV: ↓ in atorvastatin levels (↓ AUC 43%); may need ↑ dosage. • ETR: ↓ in atorvastatin levels (↓ AUC 37%); may need ↑ dosage. • EVG/c or boosted PI: not studied with COBI but expect ↑ atorvastatin levels. ↑ levels 79-836% with boosted PIs. Start at lowest dose and titrate to effect. Monitor for adverse effects. Do not exceed 20mg with DRV.
Fluvastatin	<ul style="list-style-type: none"> • Severe renal dysfunction, CrC, <30mL/min. Do not exceed 40mg/day. • Metabolized by CYP 2C9 (75%), CYP 3A4 (20%). • Not well studied; no known significant interactions with most PIs; theoretic risk of ↓ NFV levels. • ETR, DLV may ↑ fluvastatin.
Lovastatin	<ul style="list-style-type: none"> • Hepatically metabolized by first pass hydrolysis and CYP 3A4. • PIs: substantial ↑ in statin levels, high risk of adverse effects. • Do not use in patients taking PIs or EVG/c. • ETR, NVP: lovastatin concentrations may be reduced; adjust dose according to response.
Pitavastatin	<ul style="list-style-type: none"> • Extensive glucuronide conjugation by UGT1A3 and UGT2B7, and minimally by CYP2C9 and CYP2C8. • PIs: No significant change expected; titrate pitavastatin to effect. • Exception: <ul style="list-style-type: none"> • ATV/r: pitavastatin AUC ↑31% and C_{max} ↑60%. Start at lowest dose and titrate to effect. • EVG/c or boosted PI: No expected effect on ARV levels; possible decreased pitavastatin efficacy (20-26%). No dose adjustment necessary; monitor and titrate to effect.

Lipid-Lowering Medication	Considerations
Pravastatin	<ul style="list-style-type: none"> • Renal excretion and some hepatic metabolism through isomerization, hydroxylation, oxidation, and conjugation. • CrCl <30mL/min, Stage V CKD, and HD max dose: 20mg; start with 10mg daily. • PIs: variable effects; moderate ↑ pravastatin AUC and C_{max} with most. No dosage adjustment of pravastatin is required. <p>Exceptions:</p> <ul style="list-style-type: none"> • DRV/r or DRV/c: pravastatin AUC ↑ 81%. Consider alternative statin. If prescribed, use lowest possible dosage, monitor carefully. • ATV/c or ATV/r: Recommend lowest possible dosage, monitor carefully. • EFV: pravastatin AUC ↓ 40%. May need to ↑ pravastatin dosage to reach lipid goals.
Rosuvastatin	<ul style="list-style-type: none"> • Metabolized by CYP 2C9 and CYP 2C19. Mostly excreted in bile. • CrCl <30mL/min: max 10mg daily. • Asian patients may have slower metabolism: Max dose in normal kidney function is 20mg/day. • Increased rosuvastatin concentrations possible with several PIs. Use lowest dose possible. • DRV/r: rosuvastatin AUC ↑ 48% and C_{max} ↑ 144%. Use lowest possible dosage (5 mg/day), monitor carefully. • LPV/r: rosuvastatin C_{max} ↑ 366%. Consider alternative statin. If prescribed, use lowest possible dosage (5 mg/day), monitor carefully. Do not exceed rosuvastatin 10mg daily. • EVG/c: rosuvastatin AUC ↑ 38% and C_{max} ↑ 89%. Initiate rosuvastatin at lowest dose and titrate carefully. Monitor for adverse effects. • EVG plus boosted PI: increases based on interacting PI (see above for specific PI interaction).
Simvastatin	<ul style="list-style-type: none"> • Extensively metabolized by CYP 3A4. • PIs: substantial ↑ in simvastatin levels, high risk of adverse effects. • Do not use in patients taking PIs or EVG/c. • EFV: ↓ simvastatin AUC >50%. May need to ↑ simvastatin dosage to reach lipid goals. • ETR/NVP: simvastatin concentrations may be reduced; adjust simvastatin dose according to response.

Lipid-Lowering Medication	Considerations
Fibrates	<ul style="list-style-type: none"> • Used for elevated TGs. • Avoid statin and fibrate combination. • No significant interactions with ARVs expected. • LPV/r: ↓ gemfibrozil AUC 41%. Use alternative ARV; unknown if same interaction with fenofibrate.
Bile Acid Sequestrants	<ul style="list-style-type: none"> • No drug interactions with ARVs, but may interfere with absorption of ARVs. Avoid in patients who take ARVs.
Ezetimibe	<ul style="list-style-type: none"> • 2nd line – trial of niacin and bile acids first. • Not metabolized by hepatic P450 system; no significant interactions with ARVs.
Niacin	<ul style="list-style-type: none"> • Avoid in statin and niacin combination, uncontrolled gout, and DM. • Avoid in patients with cirrhosis or elevated LFTs. • Not metabolized by hepatic P450 system; no significant interactions with ARVs.
N-3 (Omega-3) Fatty Acids	<ul style="list-style-type: none"> • Can reduce TGs by 30% but need at least 3-4 grams of omega-3. • Lovaza is 100% omega-3 but is non-formulary. • Not metabolized by hepatic P450 system; no significant interactions with ARVs.
PCSK9 inhibitors – Alirocumab and Evolocumab	<ul style="list-style-type: none"> • Not metabolized by hepatic P450 system; no significant interactions with ARVs.

Recommendations for Coadministration of PIs and NNRTIs with Statin Medications

Generally safe to begin treatment with usual starting dosage
* Caution; start with low dosage, monitor effects
+ Coadministration is contraindicated

	ATV/r	DRV/r	LVP/r	RTV	COBI	EFV	ETR	EVG/c or EVG plus PI
Atorvastatin	Use lowest possible dose*	Do not exceed 20mg daily*	Use lowest possible dose*	Use lowest dose possible with careful monitoring	Use lowest possible dose. Do not exceed 20mg daily*	May need ↑ atorvastatin dosage Max 80mg/day	May need ↑ atorvastatin dosage Max 80mg/day	Do not exceed 20mg daily*
Fluvastatin	Use with caution	No interaction anticipated	No interaction anticipated	No interaction anticipated	Use with caution	May need ↑ fluvastatin dosage Max 80mg/day	May need ↑ fluvastatin dosage Max 80mg/day	Use with caution
Lovastatin	Do not use	Do not use	Do not use	Do not use	Do not use	May need ↑ lovastatin dosage Max 60mg/day	May need ↑ lovastatin dosage Max 60mg/day	Do not use
Pitavastatin	C_{max} increased by 60%	No interaction anticipated	No interaction anticipated	No interaction anticipated	Use with caution	No interaction anticipated	No interaction anticipated	Use with caution
Pravastatin	Use with caution	↑ pravastatin AUC up to 500%	No interaction anticipated	No interaction anticipated	Use with caution	May need ↑ pravastatin dosage Max 80mg/day	May need ↑ pravastatin dosage Max 80mg/day	Use with caution
Rosuvastatin	Do not exceed 10mg daily (if renal function is normal) *	Start with lowest dose and titrate while monitoring for safety*	↑ rosuvastatin C_{max} 466% Do not exceed 10mg daily*	Start with lowest dose and titrate carefully, monitoring for side effects and lipid response*	Start with lowest dose and titrate while monitoring for safety*	No interaction anticipated	No interaction anticipated	Start with lowest possible dose and titrate while monitoring for safety*
Simvastatin	Do not use	Do not use	Do not use	Do not use	Do not use	May need ↑ simvastatin dosage Max 80mg/day	May need ↑ simvastatin dosage Max 80mg/day	Do not use



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Also see product labeling for the individual ARVs.

Pain Medications: Dosage and Indications

Please refer to **Low Back Pain**, (p. 529); and **Peripheral Neuropathy**, (p. 543).

Medication	Standard Dosage	Comment
Acetaminophen	325-650 mg up to Q6H PRN Maximum dosage: 4 g per 24 hours or 2 g per 24 hours in patients with comorbid liver disease	<ul style="list-style-type: none"> • First-line analgesia in noninflammatory mild osteoarthritis (OA), low back pain (LBP), mild peripheral neuropathy (PN) because of safety profile. • Possible adverse effects: hepatotoxicity (especially if taken with alcohol), nephrotoxicity (with chronic overdose). Monitor liver and renal function when using maximum dosages. • Use caution and consider reducing total dosage for patients with comorbid liver disease or excessive alcohol intake. • Acetaminophen frequently prescribed with other pain relievers, so beware of total daily dose.
Tramadol	50-100 mg Q4H-Q6H PRN	-
NSAIDs	<p>Ibuprofen</p> <ul style="list-style-type: none"> • 600-800 mg TID-QID PRN for pain, swelling, fever • Take with food. • Schedule around the clock for inflammatory condition (e.g., inflammatory OA) or persistent symptoms. • Can titrate up as tolerated and based on risks to 800 mg TID. • Maximum dosage: 3,200 mg/day in divided doses or 1,800 mg/day for patients at increased risk of adverse effects. 	<ul style="list-style-type: none"> • For persistent noninflammatory and inflammatory OA, LBP, mild PN. • Possible adverse effects: GI bleeding, abdominal pain, rash and hypersensitivity, renal and hepatic impairment, platelet aggregation abnormalities. • Avoid use in patients with peptic ulcer disease or cirrhosis. • Avoid ibuprofen in patients with history of aspirin-induced asthma. • Increased bleeding risk with concurrent warfarin; if used, monitor closely.

Note: Some medications mentioned in this chapter may not be available on the VHA National Formulary (<https://www.pbm.va.gov/NationalFormulary.asp>). Consult VA pharmacists for alternatives.

Medication	Standard Dosage	Comment
-	-	<ul style="list-style-type: none"> Increased risk of renal impairment in patients on diuretics and those with baseline renal dysfunction, congestive heart failure, or cirrhosis.
	<p>Alternative NSAIDs congestive heart failure, or cirrhosis.</p> <p>Naproxen: 250-500 mg BID Sulindac: 150-200 mg BID Celecoxib: 200 mg QD Meloxicam: 7.5-15 mg QD</p> <p>For chronic pain, use for 2 weeks at initial dosage and reevaluate efficacy; titrate up as needed and if safe; if not effective after a 4-week trial, consider changing NSAID, or adding or changing to another intervention.</p> <p>Topical diclofenac 2-4 grams (depending on size of joint) 2 to 4 times/day, not to exceed 32 grams for all joints combined per day.</p>	<ul style="list-style-type: none"> To minimize risks, use the lowest effective dosage and try to use for short periods of time. Interferes with cardioprotective effect of aspirin. Can increase risk for myocardial infarction. May exacerbate hypertension. COX-2 inhibitors, such as celecoxib, have higher risk of cardiovascular events but fewer GI side effects than nonselective COX inhibitors. Indomethacin is associated with more adverse drug effects (ADEs) than other NSAIDs so avoid using for OA or LBP.
<p>Antidepressants: Tricyclic Antidepressants (TCAs) and others</p>	<p>Amitriptyline Start at 10-25 mg QHS; titrate upward every three days by 10 mg to 25 mg to achieve symptom relief, if tolerated; maximum daily dosage is 150 mg (use lower dosages or avoid altogether for older patients).</p> <p>Nortriptyline Start at 10-25 mg QHS; titrate upward every three days by 10 mg to 25 mg to achieve symptom relief, if tolerated; maximum daily dosage is 150 mg</p>	<ul style="list-style-type: none"> Consider for patients with comorbid depression, although antidepressants can inhibit the metabolism of ARVs. Consider for neuropathic pain; also as an adjunct in any type of LBP unresponsive to acetaminophen and NSAIDs. Drug interactions: Ritonavir (RTV) and other protease inhibitors (PIs) may increase the level of TCAs; start at low dosage, increase slowly. Monitor serum TCA levels to avoid cardiotoxicity at higher dosage levels. Addition of SSRI drugs may increase TCA concentration,

Medication	Standard Dosage	Comment
-	(use lower dosages or avoid altogether for older patients).	<p>leading to toxicity.</p> <ul style="list-style-type: none"> • Possible TCA adverse effects: anticholinergic (dry mouth, dizziness, constipation, urinary retention, blurred vision, orthostatic hypotension), extrapyramidal symptoms, incoordination, cognitive problems, sedation; risk of cardiac conduction abnormalities and overdose at higher dosages. • Increased risk of arrhythmias, especially in association with methadone. • For neuropathic pain, other potential agents include venlafaxine and duloxetine; these are inadequately studied in people with HIV infection or show limited efficacy.
Anticonvulsants	<ul style="list-style-type: none"> • Gabapentin: start at 300 mg QHS. To achieve symptom relief may increase to 300 mg BID on day two, then TID on day three, as tolerated; then increase by 300 mg per dose to maximum of 1,200 mg TID. May need to increase more slowly, every 3 or 4 days or reduce to 100 mg dose if patient experiences ADEs. • Pregabalin: start at 25-50 mg TID; may increase to 100 mg TID within 1 week as tolerated to achieve symptom relief; maximum dosage: 100 mg or 150 mg TID. • Lamotrigine: start at 25 mg every other day; titrate slowly to 200 mg. 	<ul style="list-style-type: none"> • Consider for PN. • Do not abruptly discontinue anticonvulsants as this can induce a seizure even when the individual does not have a history of epilepsy. • Gabapentin: considered first-line for HIV-SN, largely due to cost and tolerance of ADEs. See Peripheral Neuropathy, p. 543. • Common adverse effects include nausea, fatigue, cognitive impairment, somnolence, dizziness, truncal ataxia, nystagmus, peripheral edema. • To discontinue, taper over course of ≥ 7 days. • Pregabalin: sometimes better absorbed and tolerated than gabapentin. • Uncertain efficacy in HIV-related PN.

Medication	Standard Dosage	Comment
-	<p>BID over the course of 6-8 weeks.</p>	<ul style="list-style-type: none"> • Possible adverse effects include blurred vision, somnolence, dizziness, confusion, peripheral edema, tremor, and weight gain. • To discontinue, taper over course of ≥ 7 days. • May exacerbate depression. • Lamotrigine: has shown the greatest efficacy in clinical trials for HIV Sensory Neuropathies (HIV-SN) • Possible adverse effects: rash (including Stevens-Johnson syndrome), ataxia, blurred vision, dizziness, drowsiness, headache, insomnia, nausea, rhinitis, skin rash, tremor, vomiting, abdominal pain and fever. • To discontinue, taper slowly. • Drug interactions: Lopinavir/ritonavir (LPV/r) may decrease lamotrigine levels; may need to increase lamotrigine dosage for therapeutic effect.
<p>Muscle Relaxants</p>	<p>Cyclobenzaprine (Flexeril)</p> <p>5-10 mg TID prn; alternatively, 5-10 mg q HS since it is sedating; start with 5 mg doses for elderly patients and those with hepatic impairment; maximum dosage is 30 mg per 24 hours.</p> <p>Robaxin</p> <p>500 to 1000 mg QID prn; may need to start at lower dose for elderly patients; maximum dose is 8000 mg per 24 hours.</p>	<ul style="list-style-type: none"> • May be useful as adjunctive therapy for acute back pain. • Common adverse effects include headache, drowsiness, confusion, fatigue, dry mouth, dizziness, constipation. • Adverse effects include seizures if baclofen is abruptly discontinued.

Medication	Standard Dosage	Comment
-	<p>Baclofen</p> <p>5-10 mg TID or QID; start with 5 mg doses for elderly patients and those with renal impairment; maximum dosage is 80 mg QD in divided doses.</p>	-
Opiate Analgesics	<p>Options include:</p> <p>Tramadol (not a typical opiate; mechanism of action is via norepinephrine inhibition; acts in part as a central opioid agonist)</p> <p>Start with 50 mg q 6 hrs PRN pain Some patients may only tolerate 25 mg dose.</p> <p>Maximum dosage: 400 mg/day, or 300 mg/day if >70 years of age; to discontinue, taper dosage in the same way. Caution patients to avoid higher doses due to seizure and serotonin syndrome risks.</p> <p>In renal insufficiency with CrCl <30, reduce dose frequency to Q12H, and maximum dosage to 200 mg/day.</p> <p>Tapentadol also works both via norepinephrine reuptake inhibition and as a weak opioid agonist. It is better tolerated due to reduced serotonin reuptake inhibition.</p> <p>Dosing: 50-250 mg PO q12hr prn; not to exceed 500 mg/day.</p>	<ul style="list-style-type: none"> • Tramadol may cause serotonin syndrome and seizures (due to serotonin reuptake inhibition), particularly when combined with SSRIs. • Tapentadol is less likely to cause serotonin syndrome or seizures because it has less serotonin reuptake inhibition. • Use opioids for patients who have severe pain refractory to other interventions (pharmacologic or nonpharmacologic) or who cannot receive those interventions. • Start with weak opioids, assess safety, efficacy, and usage; titrate up and move to stronger opioids as needed. • Use the lowest effective dosage. • Use opioids cautiously in elderly patients. • If needed for acute flares, try to limit use to a designated short period of time. • If needed for chronic pain, try to use a sustained-release opioid (e.g., sustained-release morphine) around the clock, plus shorter acting opioids (e.g., hydrocodone) for breakthrough pain as needed. • Opioid therapy for chronic pain should use a fixed-dose schedule, not PRN dosing.

Medication	Standard Dosage	Comment
	<p>Weak opioids</p> <ul style="list-style-type: none"> • Codeine 15-30 mg every 4-6 hours; titrate up by 15 mg every 2-3 days to achieve pain relief, as tolerated. <p>Maximum dose: 360 mg in 24 hours; take with food.</p> <ul style="list-style-type: none"> • Hydrocodone + acetaminophen 5 mg/300 mg fixed-dose tablet, 1-2 tablets Q6H PRN pain. Not recommended for patients with breathing disorders. <p>Maximum dosage: eight tablets per 24 hours; six tablets for elderly patients and those with liver disease.</p> <ul style="list-style-type: none"> • Oxycodone + acetaminophen 5 mg/325 mg fixed-dose tablet (other dosages available), 1-2 tablets Q6H PRN pain. <p>Maximum dosage: 12 tablets per 24 hours; six tablets for elderly patients and those with liver disease.</p> <p>Strong opioids</p> <ul style="list-style-type: none"> • Morphine (immediate release) 10-30 mg every 3-4 hours PRN pain. • Morphine (sustained release) 15-30 mg Q12H as scheduled doses; if pain control is inadequate, consider dosing Q8H; may titrate up by 15-30 mg PRN pain. Avoid morphine if renal insufficiency because toxic metabolites may accumulate 	<p>Methadone may have utility for neuropathic pain owing to its action on N-methyl-D-aspartate (NMDA) receptors; start at low dosage and titrate slowly because of its long half-life; consult with pharmacist.</p> <ul style="list-style-type: none"> • Risk of dependence, overdose (accidental or deliberate); monitor closely. • Adverse effects include over sedation, hypotension and respiratory depression, central nervous system stimulation or somnolence, dizziness, constipation, nausea, pruritus. • Codeine and morphine can cause urticarial reactions (hives). • A subpopulation of Caucasians and Asians are unable to convert prodrug codeine to morphine, so it may not be effective. • For patients with renal and hepatic impairment, use low dosages and monitor carefully. Avoid morphine with renal impairment due to accumulation of toxic metabolites. • When prescribing opioids, remember to also give treatment for constipation (docusate and senna) as bowel motility agents. Add osmotic agents (polyethylene glycol and lactulose) as osmotic agents to hydrate stool. • Note that tramadol 37.5 mg + acetaminophen 325 mg has shown pain relief equivalent to codeine 30 mg + acetaminophen 325 mg but with fewer adverse effects (major adverse effect: headache).

Medication	Standard Dosage	Comment
	<ul style="list-style-type: none"> • Oxycodone (immediate release) 5-15 mg Q4H PRN pain. • Oxycodone (sustained release) 10 mg Q12H as scheduled doses; titrate up by 10-20 mg PRN; monitor carefully. • Methadone Consult with pharmacist. Long and unpredictable half-life; do not increase rapidly; multiple drug interactions, including oral antifungals and macrolide antibiotics). • Hydromorphone 2-4 mg Q4H PRN. • Fentanyl transdermal patch 12-100 mcg patch Q72H; a small proportion of patients will need dosing Q48H to maintain a stable blood level. Do not increase more frequently than once per week. If febrile or exposed to heat, then increased absorption, which may lead to an overdose. Dispose of so that others cannot access residual fentanyl on patch. Appropriate only for opioid-tolerant patients already on stable dosage of other opiates; start at equianalgesic (or lower) dosage; consult with pharmacist; use for chronic severe pain. 	<ul style="list-style-type: none"> • Chronic opioid therapy should incorporate an opioid use agreement that includes functional goals for outcome, not reduction of pain intensity alone.

Medication	Standard Dosage	Comment
Topical Anesthetics	Capsaicin <ul style="list-style-type: none"> • 0.025% or 0.075% cream; apply to skin over affected joint(s) or limb TID-QID. • High-dose capsaicin topical dermal patch; apply for 30-60 minutes, not more frequently than every three months and under supervision. 	Capsaicin <ul style="list-style-type: none"> • For noninflammatory and inflammatory OA, HIV-SN. • For OA or neuropathy, apply to skin over affected joint or area. • May take several days to achieve pain relief; initial application usually accompanied by sensation of heat or burning. • For neuropathy, a single capsaicin patch application can provide pain relief for up to 12 weeks.
	<ul style="list-style-type: none"> • Lidocaine dermal patch 5% Apply 1-3 patches over affected area for 12 hours QD; must be removed for 12 hours. • Diclofenac 1% topical gel Apply 2 grams to smaller joints and 4 grams to larger joints topically 2 to 4 times per day. Do not exceed 32 grams total per day. 	Lidocaine <ul style="list-style-type: none"> • Topical lidocaine may be used for neuropathic pain, but for HIV-SN it has not shown significant benefit over placebo, and is expensive; consider brief trial in patients with incomplete pain relief on other therapies. • Minimal systemic absorption. Intended for limb joints.
Colchicine Beta-tubulin Interactor	0.6 mg BID	<ul style="list-style-type: none"> • For inflammatory OA with refractory symptoms. • Avoid use for patients with renal or hepatic disease. • Use in conjunction with NSAIDs. • Consider for patients with refractory inflammatory OA, as many have calcium pyrophosphate crystals in the synovial fluid. • If used with a PI*: <ul style="list-style-type: none"> • For acute gout: reduce colchicine dosage to 0.6 mg x 1 then 0.3 mg one hour later. Dose not to be repeated earlier

Medication	Standard Dosage	Comment
-	-	<p>than three days.</p> <ul style="list-style-type: none"> For gout prophylaxis: reduce colchicine dosage to 0.3 mg QD (if on 0.6 mg BID prior to PI therapy) or reduce colchicine dose to 0.3 mg QOD (if on 0.6 mg QD prior to PI therapy).

Abbreviations: CrCl = creatinine clearance; GI = gastrointestinal; HIV-SN = HIV sensory neuropathy; LBP = low back pain; OA = osteoarthritis; PN = peripheral neuropathy; TCAs = tricyclic antidepressants

* Protease inhibitor (PI) or other strong CYP3A4 inhibitors, e.g., clarithromycin, ketoconazole, itraconazole, telithromycin, and nefazodone.



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Also see product labeling for the individual ARVs.

Psychoactive Medications: ARV Interactions

Antidepressants

Class of Medication	Considerations
SSRI	
Citalopram, escitalopram	<ul style="list-style-type: none"> • RTV causes no change in levels
Fluoxetine	<ul style="list-style-type: none"> • RTV: ↑ RTV AUC 19%, no change in C_{max}
Paroxetine	<ul style="list-style-type: none"> • DRV/r: paroxetine AUC 39%
Sertraline	<ul style="list-style-type: none"> • DRV/r: sertraline AUC and C_{min} ↓ 49% • EFV: ↓ sertraline by 39% based on clinical response
	<ul style="list-style-type: none"> • In general, when used with PIs, SSRIs should be titrated based on clinical response. • SSRI interactions with ATV/c or DRV/c are unknown, thus it is recommended to titrate SSRI dose using the lowest available dose. • SSRI with COBI: possible increase in SSRI level; initiate with low dose SSRI and titrate based on SSRI response.
SNRI	
Venlafaxine, duloxetine	<ul style="list-style-type: none"> • PIs may increase SNRI level. It is recommended to start at lowest effective dosage; monitor for adverse effects.
Tricyclic (TCA)	<ul style="list-style-type: none"> • All PIs (including ATV/c and DrV/c) may decrease TCA levels. It is recommended to start at low dosage, use lowest effective dosage; monitor for adverse effects. • EVG/c: use lowest dose of TCA and titrate carefully.
Other Antidepressants	
Bupropion	<ul style="list-style-type: none"> • EFV: ↓ bupropion AUC 55%, based on clinical response • LPV: ↓ bupropion AUC 57% • EVG/c: ↑ or ↓ bupropion possible
Buspirone	<ul style="list-style-type: none"> • All PIs or COBI-boosted agents: ↑ buspirone levels expected • Use a low dose of buspirone with caution and titrate buspirone dose based on clinical response.

Note: Some medications mentioned in this chapter may not be available on the VHA National Formulary (<https://www.pbm.va.gov/NationalFormulary.asp>). Consult VA pharmacists for alternatives.

Class of Medication	Considerations
Mirtazapine	<ul style="list-style-type: none"> • No data; RTV may ↑ mirtazapine levels • Start at low dosage, use lowest effective dosage; monitor for adverse effects.
Nefazodone	<ul style="list-style-type: none"> • RTV may ↑ nefazodone levels • Nefazodone may ↑ MVC • Start at low dosage, use lowest effective dosage; monitor for adverse effects. • MVC dosage: 150 mg BID
Trazodone	<ul style="list-style-type: none"> • RTV: ↑ trazodone AUC >200% • DRV, LPV/r: ↑ trazodone AUC EVG/c or boosted PI: ↑ trazodone possible • EVG/c or boosted PI: ↑ trazodone possible • Start at low dosage, use lowest effective dosage; monitor for CNS and cardiovascular effect.
St. John's wort	<ul style="list-style-type: none"> • Substantial ↓ in levels of most PIs, NNRTIs, and MVC • Do not coadminister.

Sedatives, Hypnotics

Class of Medication	Considerations
Benzodiazepine	
Midazolam and Triazolam	<ul style="list-style-type: none"> • Do not coadminister with PIs, COBI, or EFV due to expected significant increases in midazolam and triazolam concentration. • Higher risk of benzodiazepine adverse effects in elderly patients; avoid if possible. • For procedures, may consider single-dose IV midazolam with close monitoring.
Alprazolam, Clonazepam and Diazepam	<ul style="list-style-type: none"> • Consider alternative BZP due to possible increased concentrations.
Alprazolam and NNRTIs	<ul style="list-style-type: none"> • Monitor for alprazolam therapeutic effectiveness.
Diazepam and ETR	<ul style="list-style-type: none"> • Decreased dose of diazepam may be required; monitor for adverse effects.

Lorazepam, Temazepam, and Oxazepam	<ul style="list-style-type: none"> • Where BZD are indicated, consider using these agents. • These benzodiazepines are, in part, metabolized via non-CYP450 pathways; lower potential for interactions). • Start at low dosage, use lowest effective dosage; monitor for adverse effects.
Other Sedatives, Hypnotics	
Suvorexant	<ul style="list-style-type: none"> • Monitor for adverse effects and reduce dose if necessary. • All PIs or COBI: ↑ suvorexant expected
Zolpidem	<ul style="list-style-type: none"> • COBI: ↑ zolpidem expected • RTV: ↑ zolpidem AUC 27%

Antipsychotics

Few data on interactions between ARVs and antipsychotics

Class of Medication	Considerations
Olanzapine	<ul style="list-style-type: none"> • RTV: ↓ olanzapine AUC 53%, half-life ↓ 50% • Start at low dosage, use lowest effective dosage; monitor for adverse effects.
Quetiapine	<ul style="list-style-type: none"> • PIs or COBI-boosted agents: ↑ quetiapine expected <p>Starting quetiapine in a patient receiving a PI or COBI:</p> <ul style="list-style-type: none"> • Start quetiapine at the lowest dose and titrate up as needed. Monitor for quetiapine effectiveness and adverse effects. <p>Starting a PI in a patient receiving a stable dose of quetiapine:</p> <ul style="list-style-type: none"> • Reduce quetiapine dose to 1/6 of the original dose. Closely monitor for quetiapine effectiveness and adverse effects.
Other Antipsychotics	
Perphenazine, Risperidone, Thioridazine	<ul style="list-style-type: none"> • All PIs, ATV/c, and DRV/c: ↑ antipsychotic possible • Titrate antipsychotic dose using the lowest initial dose, or adjust maintenance dose accordingly. Monitor for toxicities.



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Prevention of HIV Transmission with Positives

Safe Conception (for HIV+ Men and Women)

KEY POINTS

- Care for serodiscordant couples should be multidisciplinary between specialists in infectious disease, reproductive endocrinology, maternal-fetal medicine and if needed behavioral health.
- Preconception care should start with counseling regarding healthy diet and exercise, screening and treatment for infectious diseases, cervical cancer screening, updating appropriate immunizations, family planning and reviewing medications for teratogenic effects.
- Encourage healthy lifestyle and abstinence from the use of alcohol, cigarettes, and recreational drugs.
- Physician-assisted fertility care includes intrauterine insemination, sperm washing with swim-up technique and In vitro fertilization with or without Intracytoplasmic sperm injection.
- Natural conception is another option for couples with focus on viral suppression of partner infected with HIV, timed-intercourse and pre- and post-exposure prophylaxis for uninfected partner.
- Seroconcordant couples with HIV are at risk for superinfection and thus should seek to obtain viral suppression and utilize the same principles as serodiscordant couples to minimize risk of transmission.



BACKGROUND

There are over 35 million people worldwide living with human immunodeficiency virus (HIV) infection and approximately 80% are persons of **reproductive age (18-44 years old)**. Infection with HIV was once a progressively fatal disease, however, since the introduction of highly active retroviral therapy (HAART or ART), HIV has now become a manageable chronic disease with improved quality of life and life expectancy. Thus it is no surprise the number of those living with HIV desiring conception is steadily increasing. Surveys in France, Canada and Switzerland report the desire for parenthood in women infected with HIV to be 32%, 25.8% and 45%, respectively. Happily, attitudes of health authorities and professional associations are beginning to change from discrimination to encouragement of reproductive health services for those infected with HIV. The United States President's Emergency Plan for AIDS Relief (PEPFAR), the American Society of Reproductive Medicine (ASRM), and the Department of Health and Human Services (DHHS) support a person's right to choose the number, timing, and spacing of their children regardless of HIV status.

Either partner can acquire HIV from vaginal intercourse, although the risk is less

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than for anal intercourse. According to the Center for Disease Control (CDC), the estimated per-act probability from an infected source of acquiring HIV from receptive or insertive penile-vaginal intercourse is 8 per 10,000 and 4 per 10,000 exposures, respectively. This number is significantly higher if the infected partner has a high viral load or if one partner has an underlying infection or genital abrasion. Special considerations exist when serodiscordant and seroconcordant couples with HIV present for pre-conceptual counseling. Serodiscordant couples may have significant concerns regarding risk of transmission to uninfected partner, vertical transmission to offspring, and potential for declining health and life expectancy. Thus, care for serodiscordant couples should be multidisciplinary between specialists in infectious disease, reproductive endocrinology, maternal-fetal medicine and, if needed, behavioral health. In this review, the available strategies to minimize the risk of HIV transmission between serodiscordant couples wishing to have biologic offspring will be discussed.

Preconception Care

Preconception care and counseling should be an integral part of primary care offered to all persons (male and female) infected with HIV of reproductive age to improve health prior to pregnancy and minimize risk of transmission to uninfected partners and potential offspring. As fertility intentions change, at least a brief discussion should be performed annually. Common counseling in preconception care include discussion of healthy diet and exercise, abstinence from alcohol, cigarettes and recreational drugs, safe sexual practices, screening and treatment for infectious diseases, cervical cancer screening, updating appropriate immunizations, family planning, and reviewing medications for teratogenic effects.

It is especially important to screen for sexually transmitted infections (STI) as persons who are HIV-negative with a STI are three times as likely of acquiring HIV after unprotected intercourse with a seropositive individual with HIV. Persons who are HIV-positive are also more susceptible to STIs likely secondary to their weakened immune system.

Samples should be taken from all potentially exposed sites (e.g., oral, rectal, vaginal, cervical) as well as urine. STI Screening should include:

- Gonorrhea
- Chlamydia
- Syphilis
- Trichomoniasis
- Human papillomavirus (HPV)
- Genital herpes
- Hepatitis B and C

Mechanisms of increased risk of HIV transmission in the setting of STIs arise from lesions of the genital skin or mucus membranes or underlying inflammation with resulting increased numbers of inflammatory cells available for infection

with HIV. Infections should be treated prior to conceiving to minimize transmission risk. In the United States and Europe, 40–80% of individuals infected with HIV are co-infected with HSV-2. Suppressive and episodic therapy for herpes simplex infection may be necessary in patients infected with HIV and may involve higher doses, more frequent administration, and longer courses than recommended for those uninfected.

Methods of Safe Conception

Physicians should counsel patients on the risks versus benefits and efficacy regarding numerous strategies available to reduce the risk of HIV transmission. Depending on the patient's personal desires, financial resources, and need for fertility assistance, options include:

- Viral suppression of a partner infected with HIV;
- Timed intercourse with or without pre- and post-exposure prophylaxis for uninfected partner;
- Intrauterine insemination (IUI);
- Sperm washing with swim-up technique with IUI; and
- In vitro fertilization with or without Intracytoplasmic sperm injection.

Natural Conception with Viral Suppression of a Partner Infected with HIV

One of the most effective means to reduce risk of HIV transmission, regardless of whether or not conception is desired, is viral suppression with antiretroviral (ARV) therapy of a partner infected with HIV along with consistent and correct condom use. The majority of studies examining the efficacy of ARV to reduce transmission risk have been prospective cohort studies. In one study that included 161 HIV serodiscordant couples on ARV with undetectable viral load for 6 months prior to trying to conceive, a total of 144 natural pregnancies occurred and 107 babies were born. Importantly, couples were instructed to limit unprotected timed-intercourse to the peri-ovulatory period and to resume condom use once pregnancy was achieved. No case of horizontal or vertical transmission occurred with 1 year of follow up post-delivery. In a meta-analysis of 11 cohorts of 5,021 heterosexual discordant couples, the rate of transmission from infected partners treated with antiretroviral therapy was 0.46 per 1000 person-years (95% confidence interval [CI], 0.19–1.09) compared with 5.64 per 1000 person-years (95% CI, 3.28–9.70) without antiretroviral therapy.

To date, there has been one randomized study of serodiscordant couples randomized to start antiretroviral therapy immediately or delay therapy until CD4 count declined or viral load increased. Those who initiated antiretroviral therapy early had a transmission rate of 0.3 per 100 person-years (95% CI, 0.1–0.6) compared with 2.2 per 100 person-years (95% CI, 1.6–3.1) in the delayed start group. This study supports that of previous cohort studies that are inherently

flawed by confounders. Taken together the data suggests that viral suppression in partners infected with HIV along with timed intercourse is a relatively effective and safe option for serodiscordant couples wishing to conceive, especially in resource-limited settings. However, it is prudent to counsel couples that even with undetectable plasma levels the risk is never zero, as HIV has been detected in semen, rectal secretions, female genital secretions, and pharynx of patients infected with HIV with undetectable plasma viral loads.

Pre- and Post-Exposure Prophylaxis in Partner Uninfected with HIV

More recent research has focused on ARV administration to the uninfected partner during the time conception is attempted or pre-exposure prophylaxis (PrEP). Ideally couples should track their menstrual cycles and use ovulation predictor kits to time when they will have intercourse without a condom and resume condom use at all other times. The largest study to date is the Partners PrEP Study Team which conducted a multicenter randomized clinical trial in Kenya and Uganda with 4747 couples who are HIV-serodiscordant in which the seronegative partner was randomized to receive daily oral tenofovir disoproxil fumarate (TDF) (n=1584), emtricitabine/TDF (FTC+TDF) (n=1579) or placebo (n=1584). Of note, all seropositive partners did not meet criteria for ARV and thus were not on medication at initiation of the study. The rate of conversion was significantly reduced from 1.99 per 100 person-years in the placebo group to 0.65 and 0.50 per 100 person-years in the TDF (p <0.001) and FTC+TDF groups (p<0.001), respectively. In a smaller study of 46 serodiscordant couples in which the female was given oral TDF daily, no women became infected with HIV and the pregnancy rate was approximately 75% at 1 year. Importantly, safety data from clinical trials have found no increased risk of birth defects or infant growth when PrEP is used during the peri-conception period.

No randomized controlled trials have examined efficacy of post-exposure prophylaxis (PEP) in serodiscordant couple trying to conceive. However, data from studies in animal models, case-control studies and observational studies following occupational exposures demonstrate low rates of seroconversion even with high rates of medication noncompliance. PEP guidelines are provided by the Center for Disease Control and Prevention (CDC) for exposures occurring in health care workers, following sexual exposure or those with high-risk practices. PEP consists of a combination of three ARV medications: two nucleoside analogues and one reverse transcriptase inhibitor. Ideally these should be initiated within hours of exposure (but must be started within 72 hours of exposure) and continued for 28 days.

CDC Recommended Guidelines for PEP

- Preferred regimen for health adults and adolescents: TDF 300 mg with emtricitabine 200 mg once daily plus raltegravir 400 mg twice daily or dolutegravir 50 mg daily
- Alternative regimen for healthy adults and adolescents: TDF 300 mg with emtricitabine 200 mg once daily plus darunavir 800 mg and ritonavir 100 mg once daily

Assisted Reproduction

Another strategy for couples who are HIV-discordant seeking to have biologic offspring is to seek assistance from a reproductive specialist. Some experts would reason that if a couple has the financial resources, physician-assisted fertility care should be first line over natural conception alone given the numerous studies demonstrating decreased risk of transmission. Additionally, patients infected with HIV often require reproductive assistance as they have increased rates of infertility compared with age-matched controls. Studies have found increased rates of tubal disease and reduced ovarian reserve in women infected with HIV and decreased sperm quality (motility and number) in men infected with HIV.

A female infected with HIV desiring fertility may not require the assistance of a reproductive specialist unless she is unable to conceive after 6-12 months of self-insemination around the time of ovulation. If unable to conceive, she should be referred to a reproductive endocrinologist for infertility evaluation. Basic evaluation should include evaluation for cervical/uterine anomaly, tubal patency, infections, and semen analysis.

In 1992, Semprini et al. published the successful use of a two-step sperm wash and swim up technique to remove the virions contained with seminal fluid and lymphocytes of whole ejaculate. The sperm is then tested for HIV with polymerase chain reaction (PCR)-based assay and intrauterine insemination (IUI) performed if negative. This technique was not recommended by the CDC until this year but has been utilized in Europe, Australia, and Canada with reported safety. A meta-analysis in 2016 reported no HIV transmission in 8,212 IUI and 1,254 in vitro fertilization (IVF) cycles, resulting in 95% confidence that the true rate is 4.5 transmissions per 10,000 IUI cycles or less. Following sperm washing the couple has the option to proceed with IUI or IVF/intracytoplasmic sperm injection (ICSI) depending on their fertility status.

In 1994, the Ethics Committee of American Society for Reproductive Medicine (ASRM) issued guidelines for the management of patients infected with HIV seeking reproductive services. In order to offer services to a patient with HIV,

clinics are required to have separate laboratory hoods and equipment for HIV-exposed specimens to minimize risk of cross contamination. Unfortunately, the majority (>80%) of U.S. fertility clinics are not equipped to offer reproductive assistance to serodiscordant couples with HIV. Reasons for limited access are likely multifactorial. In fact, until 2017, the CDC recommended against the use of sperm washing and insemination for males infected with HIV in serodiscordant couples. Hopefully with the increasing evidence of safety there will be more fertility clinics offering services to HIV-discordant couples in the U.S.A.

Seroconcordant Couples with HIV and Superinfection

HIV stimulates an immune response in the host; however, this response is not completely protective against an exposure to a new HIV challenge. HIV superinfection occurs when a known individual infected with HIV is subsequently infected with a new genetically distinct viral strain and is estimated to occur with an incidence rate of 0–7.7% per year. Prevention of additional exposure to HIV with safe sex practices or antiviral suppression discussed above can minimize risk for potential superinfection. Previous work has suggested that the risk of HIV superinfection is likely negligible when both partners are on ARV therapy and have suppressed viral loads.

Conclusion

Highly active antiretroviral therapy has significantly reduced the death rates of infected persons and HIV and is now regarded as a chronic disease. Physicians and persons infected with HIV share the responsibility for the safety of the uninfected partner and potential offspring. Thus, as physician's caring for these patients we have an obligation to counsel persons infected with HIV regarding the benefits of lifelong ARV to improve health and life expectancy and prevent maternal to child transmission.



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Sexually Transmitted Infections (STI) Screening and Resources

KEY POINTS

- HIV prevention should be a focus of routine HIV primary care.
- Prevention interventions should emphasize patients' own health, the health of their partners, and communities at large.
- Assessment of sexual and substance-use behaviors and discussion of risk reduction interventions should be address in every visit and when done properly, takes less than 5-10 minutes per visit to complete.
- Elements of the prevention evaluation and intervention include:
 - A detailed HIV transmission risk assessment, including the patient's sexual practices with each partner, and needle-use practices, if applicable
 - Screening and testing for STIs
 - Assessment of pregnancy intentions and pregnancy testing if appropriate
 - Identification and correction of misconceptions
 - Tailored prevention messages
 - Individualized interventions
 - Referrals
 - Periodic reevaluation
- Antiretroviral therapy (ARV) with maximal virologic suppression sharply decreases risk of sexual transmission of HIV, and can be an important component of an overall prevention strategy.



BACKGROUND

Sexually Transmitted Infections (STI)

The annual rate of new HIV diagnosis in the United States has fallen by 19% from 2005 to 2014. In 2015, 39,513 individuals were diagnosed with HIV and the Centers for Disease Control (CDC) reported 18,303 individuals were diagnosed with AIDS. Data from the same year indicates African American men bear the highest burden of HIV, accounting for 45% of HIV diagnoses in the United States. Hispanics/Latinos are also disproportionately affected, accounting for 24% of HIV diagnoses. Between 2004 to 2014, HIV in women was attributed to heterosexual contact or injection drug use (IDU). In addition, among men, male-to-male sexual contact is a significantly bigger driver of HIV than IDU and would emphasize that. Geographically the Southern U.S. has a higher proportion of HIV cases thought to be secondary to these regions lagging in both implementation of HIV prevention and care indicators.

Note: Some medications mentioned in this chapter may not be available on the VHA National Formulary (<https://www.pbm.va.gov/NationalFormulary.asp>). Consult VA pharmacists for alternatives.

The rates of HIV in this risk group has been rising, particularly among younger MSM and those of racial/ethnic minorities. CDC indicates the lifetime risk of men who have sex with men (MSM) of being diagnosed with HIV is:

- White MSM: 1 in 11
- Latino MSM: 1 in 4
- Black MSM: 1 in 2

<https://www.cdc.gov/nchstp/newsroom/2016/croi-press-release-risk.html>

Nearly all HIV diagnoses are attributable to risky sexual and drug-use behaviors. Each new infection originates with someone already infected with HIV; virtually all are preventable. Assessing patients' behaviors and promoting healthy changes can decrease the risk of HIV transmission. This chapter will focus on performing sexual risk assessment and making simple interventions to prevent transmission of HIV infection; this, in turn, can protect patients and their sexual and drug-sharing partners from other sexually transmitted and bloodborne pathogens, and possible HIV superinfection. Screening for sexually transmitted infections such as chlamydia, gonorrhea, syphilis are outlined in **Table 2**.

Transmission route for persons diagnosed with HIV infection in the United States:

- Men: In 2014 gay and bisexual men accounted for approximately 67% of new HIV diagnoses. According to the 2015 CDC HIV Surveillance Report, MSM accounted for 67% of the estimated new HIV diagnoses in 2015; 7% high-risk heterosexual contact; 4% injection drug use (IDU), 3% MSM and IDU.
- Women: In 2015 approximately 16% of new diagnoses were a result of heterosexual sex; 2% due to IDU.

Sources: Center for Disease Control and Prevention 2015; HIV Surveillance Report, 2015. Centers for Disease Control and Prevention: CDC 24/7: Saving Lives, Protecting People. 2015. Center for Disease Control and Prevention: Diagnoses of HIV infection in the United States and dependent areas. 2014. See References.

Sexually Transmitted Infections Epidemiology

In 2016, the CDC reported the rates of persons with STIs in the general U.S. population as follows:

- Chlamydia - 1.59 million cases
- Gonorrhea - 468,514 cases
- Primary and Secondary Syphilis - 27,814 cases
- Congenital Syphilis - 628 cases

A 2013 Tseng et al., study of U.S. military personnel examined the connection between STIs and HIV. Study participants were 80% with gonorrhea, 85% with chlamydia, and 95% with syphilis. The study concluded that nearly half of the participants were first diagnosed with a STI one year or more after HIV diagno-

sis. The high-risk sexual activities among study participants was sustained after a positive HIV diagnosis.

Screening for Risky Sexual Behaviors

The HIV clinic is an important setting for prevention efforts, to help patients decrease the risks of:

- Transmitting HIV to others via sexual or IDU behaviors
 - The riskiest sexual behavior known to transmit and contract HIV is through anal sex (CDC ref.)
- Acquiring and transmitting an STI
- Acquiring a bloodborne infection (for injection drug users) (e.g. Hepatitis C)
- HIV superinfection (**Note:** This appears to occur rarely, but can adversely affect clinical status and treatment options.)
- Unintended pregnancy

Nevertheless, studies have shown that many HIV providers do not assess transmission risks with or provide prevention messages to their patients.

For some patients, decreasing HIV transmission risks requires them to make small changes in sexual and drug-use behavior; for others, significant changes are needed. Although behavior changes can be difficult to make and to maintain, they should be encouraged. Several studies cited by CDC have shown that assessment of HIV transmission risk followed by brief prevention interventions initiated by the care provider can be effective. Various risk reduction interventions in primary care and STI clinics have resulted in:

- Increased condom use
- Safer IDU practices
- Fewer STIs
- Increased use of ARV

As with any behavior change intervention (e.g., smoking cessation, dietary modification), HIV prevention interventions need to be reevaluated and reinforced regularly. Over time, primary care providers can have a significant impact on their patients' behaviors. Health care providers often underestimate how seriously patients take their recommendations.

Addressing patients' health behaviors, particularly in the realms of sex and drug use, can be challenging or uncomfortable for some medical providers. Learning how to conduct a partner-by-partner risk assessment can reduce this discomfort. Given the preventable nature of HIV infection, HIV risk assessment and the delivery of individualized prevention messages should be routine and ongoing aspects of HIV care that are performed at the initial evaluation and periodically thereafter.

Clinicians Can Greatly Affect Patients' Risks for Transmission of HIV to Others through the Following Actions

- Performing a brief screening for HIV transmission risk behaviors
- Communicating tailored prevention messages
- Discussing sexual and drug-use behavior
- Positively reinforcing changes toward safer behavior
- Referring patients for services such as substance abuse treatment
- Facilitating partner notification, counseling, and testing
- Identifying and treating other STIs
- Initiating and supporting ARV, where appropriate

These measures also may decrease patients' risks of acquiring other STIs and bloodborne infections (e.g., viral hepatitis).

Doing prevention work with people living with HIV/AIDS can be divided into evaluation steps and management steps.



EVALUATION

- Establish rapport and conduct a quick, detailed behavioral risk assessment.
- Assess for the presence of symptomatic and asymptomatic STIs.
- Assess for use of ARV (with virologic suppression).



MANAGEMENT

- Locate patient's risk behavior along the risk continuum.
- Correct misinformation, answer questions, and educate.
- Assess patient's readiness for behavior change.
- Work toward risk reduction with an individualized prevention message based on the patient's risk behaviors and readiness to change.
- Treat STIs and supply medications, condoms, and lubricant if needed.
- Agree on what patient will do to reduce risk.
- Agree to address prevention at future visits.

The rest of this chapter will focus on these steps in more detail.



EVALUATION

HIV transmission risk assessment should be performed at the initial evaluation and periodically thereafter. For patients with significant ongoing risk factors for HIV transmission, it should be part of every visit, if possible.

Sexual Risk Assessment

- Should include an evaluation of risks of HIV transmission and risks of acquisition and transmission of other STIs (including hepatitis B virus (HBV) and hepatitis C virus (HCV) infections).

Drug and Alcohol Risk Assessment

See also **Alcohol Use**, p. 91; and **Substance Use**, p. 107.

- Illicit substance use (particularly methamphetamine use) and unhealthy alcohol use, especially binge alcohol use, are associated with unsafe sex practices, and with STI, including HIV acquisition and transmission.
- Sharing of nonsterile injection equipment can itself cause transmission of HIV and other bloodborne pathogens (including HBV and HCV).

Mental Health Assessment

See also **Depression**, p. 149.

- Serious mental illness, posttraumatic stress disorder, and depression increase the likelihood of risky sexual and drug and alcohol-use behaviors.

STI Screening/Testing

- Consider STI screening with patients who have unprotected sex, have new or multiple partners, or have been exposed to an STI. See the chapter, **Sexually Transmitted Infections (STI) Screening and Resources**, p. 55.
- The presence of an STI indicates risky sexual practices and increased risk of HIV transmission, and the potential for acquisition of different HIV strains.
- Coinfection with an STI (e.g., gonorrhea, chlamydia, syphilis, chancroid, herpes simplex virus [HSV], and trichomoniasis) can increase HIV transmission risk and is deleterious to the patient's own health.

Sexual risk assessment: To provide appropriate and specific recommendations it is important to understand the patient's risk behaviors and why he or she is engaging in them. A basic assessment should include questions about a variety of topics (see box below). Because a patient's sexual activities may vary substantially with different partners or in different circumstances, asking follow-up questions to explore the circumstances of unsafe behaviors is crucial to targeting specific risk behaviors for intervention. One very helpful way of organizing an efficient but detailed risk assessment is to ask patients to make a mental list of their most recent partners, and then explore their risk behaviors with each partner (see **Table 1** below for questions to ask).

Note: Veterans may be particularly reluctant to acknowledge same-sex sexual activities or IDU.

Military sexual trauma (MST) refers to sexual assault or repeated, threatening sexual harassment that occurred while the Veteran was in the military. VA screens for MST have revealed that about 1 in 4 women and 1 in 100 men have experienced MST. Providers should refer patients with MST to the MST Coordinator. There is a MST Coordinator at each facility to assist Veterans. See MST website, <https://www.mentalhealth.va.gov/msthome.asp>.

When interviewing patients, it is important to establish rapport to elicit truthful and complete responses and to establish a context for behavioral interventions. It often is helpful to normalize the questions as a routine part of primary care, and these topics should be discussed openly in a nonjudgmental manner.

Providers often find that systematically evaluating risk in a partner-by-partner fashion makes the risk assessment more clinical, less emotionally charged, and more comfortable for them and their patients.

Reassuring patients about the confidentiality of their responses to questions about risky behavior is a key component for establishing rapport and trust and obtaining truthful responses. The confidentiality of HIV-related information in the VA system is explicitly and specifically protected by federal law; it may be helpful at a patient's initial visit to clarify his or her confidentiality rights.

Table 1. Components of a Detailed Risk Assessment

<ul style="list-style-type: none">• Number of recent sex partners• Sex of each partner• Type of relationship with each partner (e.g., main, casual, anonymous)• HIV status of each partner• Whether patient discloses his/her HIV status to partners or potential partners• Type of sexual activity engaged in with each partner• Safer and less-safe sexual activities engaged in with each	<ul style="list-style-type: none">• Consider asking questions such as:<ul style="list-style-type: none">• “What made it more difficult for you to use condoms during this sexual encounter/with this partner?”• “What made it easier for you to use condoms during this sexual encounter/with this partner?”• Substance use (including alcohol) associated with sex
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partner; specify, oral, vaginal, anal (insertive vs. receptive)

- Use of any risk reduction techniques (e.g., condoms, serosorting*, disclosure)
- Barriers to “safer” sex (and drug-use)
- Sexual practices
- STI symptoms
- Women: Current pregnancy, desire or intention for pregnancy, contraception
- Circumstances of risky sex behaviors (e.g., while intoxicated or high, with anonymous partners, in particular settings)
- Risky drug-use practices (e.g., sharing injection equipment or nasal straws)
- Men with female sex partners: intentions for conception or fathering, contraception
- Use of ARV, with virologic suppression

*Serosorting, whereby an HIV-infected person has unprotected sex only with HIV-infected partners, likely reduces HIV transmission in settings where the HIV status of the partner is definitively known. Serosorting does not affect the risk of acquiring other STIs, including HBV and HCV infections, or the risk of reinfection with drug-resistant or more pathogenic strains of HIV.

For a more complete risk assessment questionnaire, see the Risk Assessment Battery (University of Pennsylvania and Philadelphia Veterans Administration Medical Center), reproduced in the VA Prevention Handbook; see **References**.

How to Start the Conversation

Sometimes, the hardest part of doing prevention for positives is simply starting the conversation. The CDC HIV Prevention Guidelines present examples of screening and follow-up questions that may be used in interviewing patients.

Open-ended question by clinician, similar to one of the following:

- “What are you doing now that you think may present a risk of transmitting HIV to a partner?”
- “Tell me about the people you’ve had sex with recently.”
- “Tell me about your sex life.”
- “Have you ever had sex for money or drugs?”

Screening questions* (checklist should take approximately 4 minutes):

- “Since your last checkup here,” or, if first visit, “Since you found out you are infected with HIV ...”
- “Have you been sexually active; that is, have you had vaginal, anal, or oral sex with a partner?”

If yes:

“Have you had vaginal or anal intercourse without a condom with any-

one?”

If yes:

“Were any of these people HIV negative, or are you unsure about their HIV status?”

“Have you had oral sex with someone?”

- *If yes:*
(For a male patient) “Did you ejaculate into your partner’s mouth?”
- “Have you had a genital sore or discharge, discomfort when you urinate, or anal burning or itching?”
- “Have you been diagnosed or treated for an STI?”
- “Do you know whether any of your sex partners have been diagnosed or treated for an STI?”
- “Have you shared drug-injection equipment (needle, syringe, cotton, cooker, water) with others?”

If yes:

“Were any of these people HIV negative, or are you unsure about their HIV status?”

These questions may be used in a face-to-face interview, or with a self-administered questionnaire.

*Adapted from CDC, HRSA, NIH, and HIVMA. See **References**.

STI Screening

- The presence of an STI suggests behaviors that may result in HIV transmission.
- In addition to the morbidity associated with the STI itself, the presence of an STI increases the risk of HIV transmission; diagnosis and treatment of STIs may therefore decrease HIV transmission, as well as prevent transmission of the STI.
- Screen all patients at baseline and regularly thereafter, depending on their risk factors (e.g., every 3-6 months in patients with a new sex partner or a partner who is an injection drug user); do specific tests according to sites of possible exposure; see below.
- Routinely ask patients whether they have symptoms of an STI; perform diagnostic testing for all symptomatic patients, and treat as indicated.

Table 2. Screening for STIs

Syphilis	Nontreponemal tests: rapid plasma reagin (RPR); Venereal Disease Research Laboratory test (VDRL)
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Chlamydia	<p>Urogenital infection: Nucleic acid amplification test (NAAT) on first-void urine (men and women), or cervical (women) or urethral (men) swab specimen</p> <p>Rectal infection: NAAT of rectal swab* (for all who report engaging in anal receptive sex)</p>
Gonorrhea	<p>Urogenital infection: NAAT on first-void urine (men and women), or cervical (women) or urethral (men) swab specimen; culture of male urethral or female endocervical swab specimen (for men with symptoms of urethritis, Gram stain of urethral specimen may be done)</p> <p>Pharyngeal infection: NAAT or culture of oral swab* (for all who report engaging in oral receptive sex)</p> <p>Rectal infection: NAAT or culture of rectal swab* (for all who report engaging in anal receptive sex)</p>
Trichomoniasis	Wet-mount examination or culture of vaginal secretions (for all women)
HSV	Serologic testing for HSV-2; recommended by some experts (for patients not previously diagnosed with HSV)

Adapted from CDC. Sexually Transmitted Disease Treatment Guidelines – 2006. See **References**.

*NAAT is not currently approved for this indication by the FDA. There is evidence (Meyers, 2016) that NAAT can accurately diagnose pharyngeal and rectal gonorrhea and rectal chlamydia, however, and many local public health departments have obtained Clinical Laboratory Improvement Amendment (CLIA) waivers to perform NAAT on pharyngeal and rectal swabs.

Rx MANAGEMENT

Information and education are important: Many patients have an incomplete or inaccurate understanding of how HIV is transmitted, the risks of various behaviors, and methods to prevent infection of sex partners or needle-sharing partners.

- Patient education may increase knowledge and provide motivation.
- Providers may identify and correct misconceptions.
- It is worth specifically mentioning that ARV therapy with maximal virologic suppression appears to substantially decrease HIV transmission risk but does not ensure that patients are noninfectious.
 - However, information alone is not adequate to change patients' behavior.

Brief, tailored interventions and prevention messages delivered by clinicians may help patients reduce their risks of transmitting HIV.

- These are more effective in achieving behavior change than patient education alone.

There are several models for health behavior change and various counseling techniques or programs based on those models. For further information, see the VA HIV Prevention Handbook and **References**, below. Most involve:

- Assessing the patient’s level of awareness and concern
- Helping the patient to better understand the potential consequences of his or her behavior
- Determining the patient’s readiness for change (see **Stages of Change**, below)
- Working with the patient to target a particular behavior for change
- Helping the patient bring about the desired change (this may require developing new skills [e.g., negotiation])
- Working toward further specific goals as the patient is ready

Adapted from AIDS Institute, New York State Department of Health. HIV and Primary Care: Putting Prevention into Practice; 1998.

In working with patients, it is important to assess their risk, readiness, motivation, and skills around specific behavioral changes and to work with them to prepare for these changes.

Risk Continuum

When interviewing patients, assess their positions on a continuum of risk of HIV transmission (see **Table 3**, below). Again, note that the degree or type of risk each person engages in may differ, depending on specific circumstances. Focus on specific behaviors.

Table 3. Relative Risk per 10,000 of HIV Acquisition (per act) probability

Sexual Activity (some popular terms)

Risk Factor	Relative Risk of Acquisition
Insertive fellatio (“getting head, being blown/ sucked”)	Low
Receptive fellatio (“giving head, blowing/sucking”)	Low
Insertive vaginal sex	4
Insertive anal sex (“topping”)	11
Receptive vaginal sex	8
Receptive anal intercourse (“bottoming”)	138

Parenteral

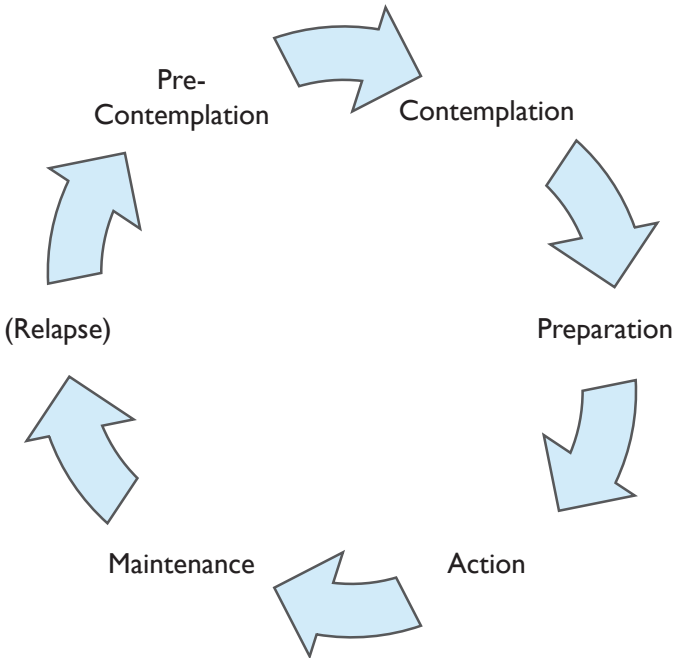
Risk Factor	Relative Risk of Acquisition
Blood Transfusion	9,250
Needle-Sharing During Injection Drug Use	63
Percutaneous (Needle-Stick)	23

Centers for Disease and Control and Prevention

Adapted from Varghese B, Maher JE, Peterman TA, et al. Reducing the risk of sexual transmission: quantifying the per-act risk for HIV infection based on choice of partner, sex act, and condom use. *Sex Transm Dis* 2002;29:38-43. Also adapted from CDC, HRSA, NIH, and HIVMA. Incorporating HIV Prevention into the Medical Care of Persons Living with HIV. *MMWR* 2003;52:RR-12.

Assess Readiness for Change

Using the Stages of Change model below, identify the patient's readiness to change risky sexual behaviors. For more on stages of change, see **Alcohol Use**, p. 91; **Substance Use**, p. 107; and **Tobacco Use**, p. 127.



Stages of Change (Transtheoretical Model)

Pre-Contemplation to Contemplation to Preparation to Action to Maintenance to (Relapse)

Work toward risk reduction: Many people may not want, or may not be willing, to adopt behaviors that entirely eliminate the risk of HIV transmission (e.g., abstinence). For most, the goal is to move from riskier activities to less-risky activities (see **Table 3**, above). Patients may do this incrementally with the support of clinicians, as they are ready and able.

Interventions may be as brief as 5-10 minutes per session. They should be repeated, refined, and reinforced at follow-up visits. For more extensive support, refer within and outside the VHA (e.g., for counseling, psychiatric treatment, and substance misuse treatment).

Individualize prevention messages and interventions. Based on the risk assessment, the clinician can help patients identify behaviors that are less risky, and can target them for intervention. The intervention should be tailored to the individual, and the goal should be attainable. Risk reduction could include:

- Disclosing one's HIV status
- Adhering to ARV with maximal suppression of HIV viremia
- Asking about partner's HIV status
- Practicing monogamy
- Reducing the number of sex partners
- Using condoms (male or female), particularly for anal or vaginal intercourse
- Having sex only with other HIV-infected partners (serosorting)
- Having no sex while intoxicated or under the influence of drugs or alcohol
- Using adequate lubrication to avoid trauma to genital or rectal mucosa
- Testing for STI regularly
- Referring partners for HIV and STI testing and counseling through Partner Services programs
- For drug users: using clean injection equipment; not sharing injection equipment

Using the risk continuum (see **Table 3**, above), help the patient identify ways toward less-risky behaviors.

An example of an intervention is the following based on the Stages of Change theory: Responses to Risk-Behavior Questions, Corresponding Stages of Behavior Change, and Possible Interventions.

Question: "How are you currently dealing with preventing HIV infection through sex or substance use?"

Type of Answer	Stage of Behavior Change	Possible Intervention
“I don’t think about it.”	Precontemplation Either unaware of risk or has no intention to change.	Contemplation of resistance by the patient. Education may enhance such awareness.
“I worry about it, but I don’t really know what to do, if anything.”	Contemplation Considers change but has no specific plan.	Education as to options. Assessment of barriers to change and discussion of benefits of change, resources, and intervention options.
“I’ve thought about it. I guess I’d like to try something.”	Prepared Ready for change. Planning for change and may have taken some initial action.	Discuss options for initiating change.
“I’ve started using condoms, but not all the time.” OR “I’ve started cleaning my works.” OR “I’m in a treatment program.” OR “I’ve been abstinent for 3 months.”	Action Initiated change.	Identify and acknowledge successful actions. Explore resources and referrals. Problem solve to help increase behavior changes.
“I’ve been using a condom now for about 6 months, nearly all the time.” OR “I’ve started using a syringe exchange program.” OR “I’m going to therapy every week.”	Maintenance Adopted a new behavior.	Evaluate factors supporting and potentially discouraging maintenance.

<p>“I was really good for a long time, but then I started seeing somebody new and I just stopped. I’m not sure it was the right thing to do.” OR “I went cold turkey for a while, but I ran into some old friends who were using, and I picked up again.” OR “I sometimes have a drink and it leads to casual sex.”</p>	<p>Relapse Time or changing factors result in discontinuing adopted behavior.</p>	<p>Evaluate the need for reinitiating behavior. Discuss factors influencing cessation of desired behavior. Repeat education-decreasing alcohol use to lower risk levels to decrease sexual risk. Make appropriate referrals as needed for treatment (e.g., Mental Health; Addiction treatment).</p>
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Reprinted with permission from AIDS Institute, New York State Department of Health. HIV and Primary Care: Putting Prevention into Practice; 1998. Data from Prochaska JO, DiClemente CC, Norcross JC. In search of how people change. Applications to addictive behavior. *Am Psychol.* 1992 Sep;47(9):1102-14.

Providers should give information, education, and support regarding ways to reduce risk.

Practical Supports

Prescribe condoms (male and female condoms are available on the VHA National Formulary). Refer to substance use treatment programs as needed, and needle exchange programs if available.

Refer patients, as needed, to VHA or community resources, for:

- More intensive risk reduction counseling and intervention
- Instruction on practical skills (e.g., correct condom use, negotiation skills)
- Substance use treatment
- Mental health treatment
- Assistance with social problems (e.g., lack of money or housing)
- Case management, social services
- Support around other problems that contribute to risky behaviors
- Partner Services through health department (an important resource for partners and is appropriate for patients with HIV+ who are newly diagnosed and/or engaging in high risk sexual risk behaviors that may result in HIV transmission, including evidence of a new STI)

Providers should counsel their patients about Pre-exposure prophylaxis, or PrEP, availability so they can inform partners. See **PrEP for Sexual and Drug Partners**, p. 81.

Follow Up:

- Reassess HIV transmission risks at each visit
- Identify and correct misconceptions
- Answer the patient’s questions

- Reinforce focused prevention messages
- Give encouragement and positive reinforcement for positive changes in risk behaviors
- Identify next steps for further risk reduction
- For patients who continue risky behaviors, elicit their beliefs and attitudes about their behaviors
- Offer counseling and develop further intervention, based on their motivation and their current stage on the change continuum



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Pregnancy and HIV-Limiting Transmission to Fetus

KEY POINTS

- All women should be offered human immunodeficiency virus (HIV) testing and counseled on the benefits of early diagnosis and treatment to reduce mother-to-child transmission.
- The Veterans Health Administration (VHA) policy on HIV testing is opt-in which requires verbal informed consent prior to HIV testing.
- Early testing allows early identification and treatment with antiretroviral therapy to reduce risk of mother-to-child transmission and optimize maternal health.
- All pregnant women with HIV should be on triple antiretroviral therapy.
- Intravenous zidovudine (AZT) therapy should be initiated intrapartum 3 hours before delivery if the viral load is >1000 copies/mL to decrease mother-to-child transmission.
- Cesarean delivery is recommended if the viral load is unknown or if the viral load is >1000 copies/mL to reduce mother-to-child transmission.
- Postpartum women with HIV should be continued on antiretroviral (ARV) therapy, offered contraception, and should not breastfeed. These women should be followed closely for adherence and screened for postpartum depression.
- Infants born to HIV-positive mothers should be started on post-exposure prophylaxis immediately after delivery and continued for 4-6 weeks.



BACKGROUND

Infection with the human Immunodeficiency virus (HIV) was once a progressively fatal disease. However, since the introduction of highly active antiretroviral therapy (HAART or ARV therapy), HIV has now become a manageable chronic disease with improved quality of life and increased life expectancy. While the number of new cases of HIV infection has declined, the number of those living with HIV is increasing. According to the Centers for Disease Control and Prevention (CDC), approximately 230,360 women in the United States were living with HIV at the end of 2014. Women are more likely to acquire HIV through heterosexual vaginal intercourse (74%), but may also become infected through anal sex or IV drug use. It is estimated that 11% of women infected with HIV in the United States are undiagnosed. Thus, pregnancy and prenatal care present an opportunity for diagnosis, counseling, and treatment.

- All pregnant women should be offered HIV testing and counseled on the benefits of early diagnosis and treatment to reduce mother-to-child transmission (MTCT).
- The CDC, the American Academy of Pediatrics (AAP), and the American College of Obstetrics and Gynecology (ACOG) recommend using the

Note: Some medications mentioned in this chapter may not be available on the VHA National Formulary (<https://www.pbm.va.gov/NationalFormulary.asp>). Consult VA pharmacists for alternatives.

opt-out screening strategy for HIV in pregnancy where all women are informed that they will be tested for HIV in their initial blood work and have the option of declining testing.

- The Veterans Health Administration (VHA) policy on HIV testing is opt-in which requires verbal informed consent prior to HIV testing.
- ACOG recommends repeat HIV testing in the 3rd trimester of pregnancy for high-risk women.
- A high-risk pregnancy involves a woman or baby who is more likely than usual to become ill or die or when there are more complications than usual before or after delivery.

More information regarding VA policy of HIV testing can be found at: <https://www.hiv.va.gov/provider/topics/testing-and-counseling.asp>.

Mechanisms of Mother-to-Child Transmission (MTCT)

The goal of caring for pregnant women with HIV is prevention of MTCT. Ninety percent of HIV transmission in infants occurs through perinatal MTCT.

- Antepartum (trans-placental)
- Intrapartum (disruption of placental-blood barrier or trans-vaginally)
- Postpartum (breast feeding)

Studies have demonstrated several in utero routes of HIV transmission. HIV may infect placental immune cells, i.e. fetal placental macrophages (Hofbauer cells), dendritic cells, as well as placental trophoblasts. To reduce the mother-to-child transmission with pregnant women infected with HIV, monitor the mother's immunological and virological levels and resistance testing. Base decisions about therapies and drug regimens on test results.

Rates of MTCT in utero are estimated at 6-13% in those that did not receive ARV therapy but did receive intrapartum prophylaxis. During labor, the mechanisms of cervical effacement and dilation as well as uterine contractions can lead to a breakdown of the blood-placental barrier and increase viral loads in the amniotic fluid and vaginal mucosa. During vaginal delivery, the infant will be in direct contact with infected secretions and maternal blood. Rates of MTCT can be reduced to less than 2% with the use of antepartum ARV therapy, intrapartum ARV therapy, when indicated, and postpartum prophylaxis in the newborn. Additionally, avoidance of breastfeeding has been shown to decrease the rate of transmission to the newborn by 30-50%.

Antepartum Management

Prenatal Care

At the first prenatal visit, a thorough history should be conducted to assess for past obstetric and gynecologic history, current and recent sex partners, drug and

alcohol use, mental health disorders, intimate partner violence, and any prior ARV therapy and treatment or prophylaxis for opportunistic infections. Patients should undergo blood work, PAP screening, screening for sexually transmitted infections (STI), and ultrasound to confirm intrauterine pregnancy. Patients who are HIV-positive are more likely to screen positive for STIs, mental health disorders, and intimate partner violence. They are also more susceptible to STIs, likely secondary to their weakened immune system. Treatment of infections and referrals to appropriate subspecialists should be made as indicated. Counseling should include continued safe sexual practices and consistent condom use.

In collaboration with an infectious disease specialist, plasma HIV RNA (viral load) should be assessed at the initial prenatal visit, 2-3 weeks after initiation of ARV therapy, monthly until viral load is undetectable, and then every 3 months during pregnancy. The viral load should then be reassessed at 36 weeks to guide counseling regarding mode of delivery. CD4 count should be assessed at the initial visit to determine the need for opportunistic infection prophylaxis and then every 3-6 months during pregnancy. HIV drug resistance studies should also be performed prior to starting ARV therapy.

Although no cases of vertical transmission following invasive prenatal testing have been reported, patients should be counseled about the theoretical risk of transmission and invasive procedures should be avoided if possible. Amniocentesis should only be performed after weighing the risks and benefits and following consideration of noninvasive methods of risk assessment, such as serum screening, nuchal translucency, and noninvasive prenatal testing.

Highly Active Antiretroviral Therapy

In 1992, a retrospective study demonstrated the safety of antepartum zidovudine (AZT) use in 45 women and 46 infants. This study was followed by a multicenter randomized, double-blind, placebo-controlled trial (AIDS Clinical Trials Group Protocol 076 Study Group) of AZT use (antepartum, intrapartum and neonatal postpartum) in 477 pregnant women. The status of HIV infection was followed for 363 births, which showed that AZT use resulted in a 67.5% relative reduction in the risk of MTCT ($p = 0.00006$). Since that time, triple combination ARV therapy in pregnancy has been shown to reduce MTCT to less than 2%.

The Panel on Treatment of Pregnant Women with HIV Infection and Prevention of Perinatal Transmission (the Panel) review the literature and publish updated guidelines for health care providers, patients, and policy makers. According to this panel, women who are on ARV therapy before they become pregnant with good viral suppression should remain on the same regimen unless they are taking regimens containing didanosine, stavudine, or treatment-dose ritonavir, and (until more data are available) elvitegravir/cobicistat.

Table 1. Initial Combined Regimens for Antiretroviral-Naïve Pregnant Women

Preferred Two-Nucleoside Reverse Transcriptase Inhibitor (NRTI) Backbones

Drug	Dosing and Side Effects
Abacavir/ lamivudine (ABC/3TC)	Available as Fixed-Drug Combination (FDC). Once daily administration. ABC should not be used in patients who test positive for HLA-B*5701 because of risk of hypersensitivity reaction. ABC/3TC with ATV/r or with EFV is not recommended if pretreatment HIV RNA is >100,000 copies/mL.
Tenofovir disoproxil fumarate/ emtricitabine (TDF/FTC) or Tenofovir disoproxil fumarate/ lamivudine (TDF/3TC)	TDF/FTC available as FDC. Either TDF/FTC (co-formulated) or TDF with separate 3TC can be administered once daily. TDF has potential renal toxicity. Thus, TDF-based dual NRTI combinations should be used with caution in patients with renal insufficiency.

Alternative Two- Nucleoside Reverse Transcriptase Inhibitor (NRTI) Backbones

Drug	Dosing and Side Effects
Zidovudine/ lamivudine (AZT/3TC)	Twice-daily administration. Increased potential for hematologic toxicities. Available as FDC.

Preferred Protease Inhibitor (PI) Regimens

Drug	Dosing and Side Effects
Atazanavir/ ritonavir (ATV/r) plus a Preferred Two-NRTI Backbone	Once-daily administration. Maternal hyperbilirubinemia, recommend neonatal bilirubin monitoring. Cannot give with proton-pump inhibitors. Avoid methylergonovine as PIs inhibit CYP3A4 and may potentiate effects.
Darunavir/ ritonavir (DRV/r) plus a Preferred Two-NRTI Backbone	Twice-daily administration is necessary in pregnancy.

Alternative Protease Inhibitor (PI) Regimens

Drug	Dosing and Side Effects
Lopinavir/ ritonavir (LPV/r) plus a Preferred Two-NRTI Backbone	Twice-daily administration is necessary in pregnancy. More nausea than with preferred regimens. Recommend increase dosage in third trimester (i.e., LPV 600 mg plus RTV 150 mg twice daily without regard to meals or LPV 500 mg plus RTV 125 mg twice daily without regard to meals) should be used in the second and third trimesters, especially in PI-experienced pregnant women and women who start treatment during pregnancy with a baseline viral load >50 copies/mL. Avoid methylegonovine as PIs inhibit CYP3A4 and may potentiate effects.

Preferred Integrase Inhibitor (INI) Regimen

Drug	Dosing and Side Effects
Raltegravir (RAL) plus a Preferred Two-NRTI Backbone	Twice-daily administration. Allows for rapid viral load reduction (good option if starting late in pregnancy).

Alternative Integrase Inhibitor (INI) Regimen

Drug	Dosing and Side Effects
Dolutegravir (DTG) plus a Preferred Two-NRTI Backbone	Once-daily administration. Available as FDC (with ABC and 3TC, requiring HLA-B*5701 testing).

Alternative (Non-Nucleoside Reverse Transcriptase Inhibitor (NNRTI) Regimens

Drug	Dosing and Side Effects
Efavirenz (EFV) plus a Preferred Two-NRTI Backbone	Once-daily administration. Preferred regimen in women who require co-administration of drugs with significant interactions with preferred agents who are not eligible for RPV.
Rilpivirine/tenofovir disoproxil fumarate/ emtricitabine (RPV/ TDF/FTC) (or RPV plus a Preferred Two-NRTI Backbone)	Once-daily administration. RPV not recommended with pretreatment HIV RNA >100,000 copies/mL or CD4 cell count <200 cells/mm ³ . Do not use with proton pump inhibitors.

Adapted from <https://aidsinfo.nih.gov/guidelines>.

Tenofovir alafenamide (TAF) is now an alternative to TDF in many widely-used FDC medications for the treatment of HIV. As of November 2017, the U.S. Department of Health and Human Services guidelines state that there is insufficient data on human use of TAF in pregnancy to inform a risk determination for birth defects or miscarriage. Furthermore, no pharmacokinetic studies of TAF have been reported in pregnant women and no data are available on placental or breast milk passage of TAF in humans, <https://aidsinfo.nih.gov/guidelines/html/3/perinatal/495/tenofovir-alafenamide--vemlidy--taf->

Viral Load and Mode of Delivery

The following recommendations regarding timing of delivery are in accordance to ACOG, the CDC, and available best practice guidelines. All women should be counseled regarding the maternal risks associated with cesarean delivery and the available evidence regarding neonatal transmission rates. Ultimately, if a patient declines cesarean delivery, patient autonomy should be respected and all efforts to reduce MTCT employed in these circumstances.

Known Women Who are HIV Positive on ARV Therapy (Recent HIV RNA Viral Load <1000 copies/ml)

Women who are HIV-positive remain on their ARV therapy during labor. If delivery is required in this setting, viral load can be used to guide delivery approach. In women with a recent viral load demonstrating <1000 copies/ml, attempted vaginal delivery with or without intrapartum AZT can be considered given low risk for intrapartum vertical HIV transmission. If a woman requires cesarean delivery for obstetric indications, cesarean delivery should not be electively performed before 39-weeks gestation if the viral load is <1000 copies/ml and the patient demonstrates consistent ARV therapy use. Several recent studies have shown that addition of AZT to women with viral load < 1000 copies/ml did not add any additional benefit to reduce MTCT, thus it is up to the patient and provider to develop an individualized delivery plan regarding intrapartum AZT therapy.

Known Women who are HIV Positive: (Recent Viral Load >1000 copies/ml), unknown or No Recent Viral Load)

If delivery is required in this setting, scheduled cesarean delivery is recommended to reduce risk of MTCT. Delivery is recommended at 38-weeks gestation to decrease risk of labor and spontaneous rupture of membranes (SROM). There is insufficient evidence to determine whether cesarean delivery following onset of labor or SROM will decrease the risk of MTCT. In addition to standard peri-operative antibiotics, all women should receive peri-operative AZT as outlined below.

Suspected Women who are HIV Positive (Screen Positive in L&D Prior to Completion of Confirmatory Testing)

Given these women have a presumptive diagnosis of HIV (pending confirmatory testing) and are not on antiviral therapy, counseling should be provided regarding the unconfirmed HIV results and potential risks of intrapartum MTCT of HIV. If delivery is required prior to return of confirmatory testing, cesarean delivery should be recommended for such women to reduce risk for MTCT. All women in this setting should receive peri-operative AZT as outlined below.

Intrapartum Management

All women with HIV viral loads >1000 copies/mL, unknown or suspected HIV infection (screen positive prior to completion of confirmatory testing) in active labor, preterm labor, or with anticipated cesarean delivery, should receive intrapartum zidovudine therapy (AZT) three hours prior to anticipated delivery using the protocol below:

Zidovudine (AZT)

- Initial Load Infusion
 - Intravenous infusion of AZT 2 mg/kg body weight over 1 hour.
- Maintenance Infusion
 - Following initial load, continuous infusion of AZT 1 mg/kg body weight should be continued until delivery.

In women with viral loads <1000 copies/mL attempting vaginal delivery, use of fetal scalp electrodes, operative delivery and episiotomy should be avoided. Additionally, if hemorrhage becomes an issue, caution should be taken when using methylergonovine if the ARV therapy includes a PI (CYP3A4 inhibitor).

Rx MANAGEMENT

Postpartum Management

Women with newly diagnosed HIV should have infectious disease consultation obtained to guide post-partum treatment, if any, pending return of confirmatory HIV testing.

Breastfeeding

Postpartum the CDC and ACOG recommend avoidance of breastfeeding in developed countries and advocate exclusively bottle-feeding to further reduce the risk of MTCT.

Contraception

Counseling regarding contraception use should begin during the antepartum period to allow for adequate discussion and planning. According to the World Health Organization, all contraceptive methods are safe to use in women with HIV infection. A good option for patients is Depo-Provera® (depot medroxy-progesterone acetate, or DMPA). DMPA or the Depo-shot is highly effective because of the massive doses of progestins involved. Other options are the vaginal ring or the transdermal patch hormonal contraceptives.

If a woman prefers to be on oral contraceptives, she should be counseled about the potential decreased efficacy or increased toxicity that may occur when taking certain ARV therapy agents. All women with HIV may also consider permanent sterilization at the time of cesarean or immediately postpartum if they are satisfied with parity.

Infant Post-Exposure Prophylaxis

All infants born to women with HIV require close monitoring and post-exposure prophylaxis (PEP). Recommendations for low risk infant (maternal antepartum ARV therapy use with undetectable viral loads at delivery) consist of 4 weeks of oral AZT. Recommendations for all other high risk infants (maternal detectable viral load or unknown viral load) are for combination prophylaxis with nevirapine (NVP) and AZT. There are several alternative dosing recommendations for NVP such as: 1st dose of Nevirapine immediately after birth, 2nd dose at 48 hours and 3rd dose at 96 hours, single dose or 2-week daily course, however all recommend daily zidovudine for the first 6 weeks of life.

Conclusion

Care for women with HIV during pregnancy requires the cooperation of specialist in HIV care, high-risk obstetricians, and often mental health providers. Early diagnosis of HIV in pregnancy allows for early initiation of combined ARV therapy (treatment as prevention), which has significantly reduced the risk of mother-to-child transmission. Combined antepartum ARV therapy along with intrapartum AZT therapy and/or scheduled cesarean delivery have decreased risk of MTCT to <2%. The CDC estimates that between 1994 and 2010, 21,956 new cases of perinatally acquired HIV infections were prevented in the United States.



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PrEP for Sexual and Drug Partners

KEY POINTS

- Pre-exposure prophylaxis (PrEP) is a combination pill medication used to reduce HIV acquisition in high-risk adults.
- Higher rates of PrEP daily adherence are associated with better efficacy to prevent HIV.
- A sexual history should be obtained from all patients to determine sexual partners and sexual behaviors which may contribute to HIV acquisition risk.
- PrEP should always be used in combination with safer sex practices and harm reduction practices to reduce the risk of acquiring HIV.
- Quarterly follow-up visits are essential for continual evaluation of adherence, testing for HIV and sexually transmitted infections and counseling for HIV risk-reduction behaviors.

Note: Current information on VHA policy, guidelines, and tools related to HIV Preexposure Prophylaxis (PrEP) can be found online at <https://www.hiv.va.gov/provider/topics/prep-index.asp>.



BACKGROUND

- Human Immunodeficiency virus (HIV) is a major public health problem affecting the United States and Veteran population. The U.S. Centers for Disease Control and Prevention (CDC) estimates an incidence of approximately 40,000 new HIV infections in 2015. The Veterans Health Administration (VHA) estimates that over 28,000 patients were treated at a VA facility for HIV in 2016. Because the VHA is the nation's largest single HIV care provider, it is presented with a unique opportunity to participate in HIV prevention and sexual health counseling.
- Several trials were instrumental in establishing the efficacy of PrEP in populations at risk of HIV infection. Overall, higher rates of adherence to PrEP were associated with better efficacy when provided with risk-reduction counseling and condoms.

Clinical Trial	Population	Efficacy (by Blood Detection of Drug Measures)
iPrex (TDF/FTC vs. placebo)	Men who have sex with men	92% (40-99%)
Partners PrEP (TDF vs. TDF/FTC)	Men who have sex with men	TDF: 86% (67-94%) TDF/FTC: 90% (58-98%)
TDF2 (TDF/FTC vs. placebo)	Heterosexual men and women	TDF detected: 85%

Note: Some medications mentioned in this chapter may not be available on the VHA National Formulary (<https://www.pbm.va.gov/NationalFormulary.asp>). Consult VA pharmacists for alternatives.

BTS (TDF)	Injection drug users	74% (17-94%)
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- In 2012, the U.S. Food and Drug Administration approved tenofovir disoproxil fumarate/ emtricitabine (TDF/FTC, Truvada®) in combination with safer sex practices for pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1 infection in adults at high risk. The CDC published guidelines in 2014 to assist providers in assessing and educating patients on the use of PrEP and safer sex practices.

Target Populations

- In accordance with the CDC guidelines, VHA recommends that PrEP be considered in the following patients:
 - Sexually active men who have sex with men (MSM) at high risk of HIV acquisition
 - Transgender women who have sex with men
 - Heterosexually active men and women at substantial risk of HIV acquisition
 - Heterosexually active men and women whose partners are known to have HIV infection
 - Adult people who inject drugs at substantial risk of HIV acquisition
- Behaviors or conditions that put an individual at substantial risk of HIV acquisition include:
 - History of inconsistent or no condom use
 - High number of sex partners
 - Having a sexual partner who is HIV-positive
 - Diagnosis or report of a sexually transmitted infection (STI) in the last 6 months
 - Commercial sex work
 - Having an injecting partner who is HIV-positive
 - Sharing injection equipment



EVALUATION

- During the clinic visit, evaluation for PrEP should include assessments of the following:
 - Risk behaviors
 - Substance use and alcohol use behaviors
 - Symptoms or recent history of STIs
 - Symptoms of acute HIV
 - Mental health screening

- Adherence to other medications
- A sexual history should be a part of all primary care clinic visits to determine number of sexual partners (same-sex and opposite sex) and sexual behaviors which may contribute to HIV risk. Patients should be informed that the information is confidential and will be used for assessment of their sexual health care.
- Patients not deemed to be eligible to receive HIV PrEP should be educated about non-occupational post-exposure prophylaxis (nPEP). See **Post-exposure Prophylaxis CDC guidelines**, <https://www.cdc.gov/mmwr/preview/mmwrhtml/rr5402a1.htm>.
- Alternatively, patients who repeatedly receive nPEP should be evaluated for PrEP. If eligible, PrEP can be initiated after completion of the 28-day course of PEP.
- Optional ICD-10-CM codes relevant to PrEP evaluation can be found at the HIV/AIDS-HIV PrEP resource page for VA health care providers. (<https://www.hiv.va.gov/provider/topics/prep-index.asp>.)

Clinicians should introduce the topic of sexual health in a non-judgmental manner which helps the patient feel as comfortable as possible. An example of full risk assessment can be found in the **Prevention of HIV Transmission with Positives** chapter of the handbook (see p. 45).

Example dialog: "I would like to ask you a few questions about your sexual health as part of my assessment of your overall health."

"In the past 6 months:

- *Have you had sex with men, women, or both?*
- *How many partners have you had sex with?*
- *How many of your partners were known to be HIV-positive?*
- *How many times do you or your partner use a condom when engaging in sex?*
- *Have you ever exchanged money, alcohol, or drugs for sex?*
- *Have you used drugs not prescribed to you by a health care provider?*
- *Have you ever used injection drugs?"*



SCREENING

HIV Testing

- HIV infection must be ruled out before PrEP is initiated:
- HIV testing with a 4th generation Ag/Ab serum test or point-of-care, FDA-approved fingerstick blood test is recommended if possible. Refer to CDC PrEP guidelines for algorithm with HIV testing interpretation.
- Oral rapid tests are **not** recommended because of low sensitivity.

- An HIV RNA viral load may be ordered to rule out an acute HIV infection.
- HIV testing should be done within one week of PrEP initiation.
- Ask about symptoms of acute HIV including fever, fatigue, myalgia, skin rash, headache, night sweats and diarrhea.

Additional Lab Testing

- Hepatitis B status must be assessed via serology before PrEP is initiated:
- Patients negative for evidence of infection or immunity should be vaccinated.
- Patients positive for evidence of infection should be referred to an HIV or HBV specialist before initiating PrEP. Both TDF and FTC are active against hepatitis B and could cause reactivation of Hepatitis B infection if TDF/FTC (Truvada®) is abruptly discontinued.
- Renal function must be calculated (using Cockcroft-Gault formula) and impairment should be ruled out. PrEP is contraindicated in patients with creatinine clearance (CrCl) less than 60 ml/min, and should be used only with caution and frequent monitoring in patients with CrCl 60-90 ml/min.
- Sexually transmitted infections screening should be performed for syphilis, gonorrhea, and chlamydia. If positive, patients can be treated while receiving PrEP.
- Pregnancy tests should be ordered for women of child-bearing age.

Rx MANAGEMENT

Initiating PrEP

- **The primary goal of HIV PrEP is prevention of HIV infection with full adherence and no or minimal adverse effects.**
- TDF 300 mg/FTC 200 mg (Truvada®) once daily is recommended for MSM, heterosexually active men and women and IDU who are eligible to receive HIV PrEP.
 - Common side effects include nausea, flatulence, rash, and headache.
 - Serious side effects include decreased bone marrow density, decline in renal function and lactic acidosis.
- VHA recommends giving a 90-day supply of FTC/TDF (Truvada®) to promote adherence. No refills should be included to promote follow-up clinic visits. Reassessment for adherence, testing for HIV and sexually transmitted infections, and counseling for HIV risk-reduction behaviors should be performed before a new prescription is provided to the patient.

- Patients can be prescribed condoms when appropriate to promote safe sex and reduce HIV risk.
- The time from initiation of PrEP to maximal protection against HIV infection is not precisely known. Patients should be advised to be especially adherent to condom use and safe-sex practices during the first 2-3 weeks of initiating prophylaxis.
- FTC/TDF (Truvada®) is a Pregnancy Category B medication and is approved for PrEP in women of childbearing age at substantial risk of HIV acquisition. Risks and benefits should be discussed if a decision is made to continue PrEP during pregnancy as limited data is available regarding the effects of TDF/FTC (Truvada®) on a developing fetus.
- Although the package insert recommends against breastfeeding while taking FTC/TDF (Truvada®), data from babies born to mothers who are HIV-infected suggest limited drug exposure to FTC or TDF. Risk and benefits should be discussed with the patient when making a decision to begin or continue PrEP while breastfeeding.

Follow-up Appointments

- Patients should be seen in clinic and reassessed every 3 months. An optional 1-month telephone follow-up visit to assess for adherence and tolerability can be scheduled.
- Clinic visits should include assessment of adherence to TDF/FTC (Truvada®), side effects, symptoms of acute HIV infection, sex history since last clinic visit and alcohol and drug-use risks.
 - Adherence can be improved with use of pillboxes, phone alarms, social support or scheduling the pill to be taken at a convenient time each day.
- Lab testing should include HIV testing, creatinine, STI tests (e.g. gonorrhea, chlamydia and syphilis) and pregnancy testing if indicated.
- Education should include reinforcement of potential benefits and limitations of TDF/FTC (Truvada®) and risk reduction counseling. Risk reduction counseling should include the following highlights:
 - Create and maintain a trusting, non-judgmental and confidential environment for discussion of sexual and substance use behaviors.
 - Build an ongoing dialogue with patients regarding their risk behavior and encourage changes in risky behaviors where appropriate.
 - Reinforce the fact that PrEP is most effective in preventing HIV infection, when taken with full adherence in conjunction with other prevention methods (e.g. consistent condom use, discontinuation of drug injection use or never sharing injection equipment) confers very high levels of protection).

- A decision should be made with the patient at every clinic visit to determine whether to continue PrEP after assessment of HIV and laboratory tests, adverse effects, adherence, and ongoing risks of HIV infection.

Discontinuing PrEP

- PrEP should be discontinued if the patient's HIV acquisition risk decreases, FTC/TDF (Truvada®) is not tolerable, or if the patient is poorly compliant with medication adherence and/or clinic visits. PrEP may also be discontinued by the patient for personal reasons. Document the patient's HIV status, reason for discontinuation, medication adherence and recent risk behaviors for future reference.
- If the patient tests positive for HIV, stop PrEP immediately, and refer the patient urgently for HIV care as TDF/FTC is not adequate to treat HIV infection. Counsel the patient on utilizing risk-reduction strategies to reduce risk of transmitting HIV.
- If the patient has active hepatitis B infection, consult with a specialist before discontinuing TDF/FTC – a flare of hepatitis B may occur.



WHEN TO REFER

- Mental health services can be instrumental in reducing and modifying risky sexual behavior which can lead to voluntary discontinuation of PrEP. Mental health services can also assist in identifying barriers which may impede adherence.
- Referrals to mental health services, social services and substance use treatment programs can be made for patients with active drug or alcohol use when indicated.
- Referral to infectious diseases services should be made if PrEP patients are diagnosed with HIV infection.

Potential Drug-Drug Interactions with HIV PrEP

- Drugs that reduce renal function or compete for active renal tubular secretion can be increased when used in conjunction with TDF, or concentrations of TDF may be increased. Dose-related renal toxicities should be monitored. No data are available for interactions with emtricitabine.



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Behavioral Health

Substance Use

Alcohol Use

KEY POINTS

- Alcohol misuse is the fourth leading preventable cause of death in the United States.
- Alcohol misuse is common among patients with HIV.
- Self-reported non-adherence to antiretroviral therapy is common with alcohol misuse.
- Alcohol misuse, smoking, and depression (see **Tobacco Use**, p. 127 and **Depression**, p. 149) are commonly comorbid with HIV.
- Screening, followed by brief counseling interventions or treatment, can decrease drinking and improve health outcomes.
- At the initial visit and at least annually thereafter, all patients should be screened for alcohol misuse with the Alcohol Use Disorders (AUD) Identification Test-Clinical Utility (AUDIT-C, see below) alcohol screening tool.
- Evaluate and treat at-risk and disordered alcohol drinkers with the four A's: Ask, Assess, Advise, and Assist.
- Consider referrals to VA substance use treatment programs such as (VA) Alcohol and Drug Dependence Rehabilitation Program that provides medical, social, vocational, and rehabilitation therapies to eligible alcohol and drug dependent Veterans.

Generally consider pharmacotherapy for alcohol use (see **Table** below).



BACKGROUND

Alcohol Use Disorder

In the DSM-5, alcohol abuse and alcohol dependence are now diagnosed as a single disorder called Alcohol Use Disorder with mild, moderate, and severe sub-classifications. Anyone meeting any two of the 11 criteria during the same 12-month period would receive a diagnosis of AUD. The severity of an AUD is based on the number of criteria met.

Veterans with HIV*

34% of Veterans with HIV have ever been diagnosed with an Alcohol Use Disorder

*Veterans with HIV in VHA care in 2017 who ever had a VHA diagnosis of selected comorbid conditions prior to or during the target calendar year.

Note: Some medications mentioned in this chapter may not be available on the VHA National Formulary (<https://www.pbm.va.gov/NationalFormulary.asp>). Consult VA pharmacists for alternatives.

DSM-5

Page 92 was removed due to copyright permissions. See the printed manual or American Psychiatric Association Diagnostic and Statistical Manual of Mental Disorders at NIH Publications for the DSM-5 questions to establish drinking levels.

<https://www.psychiatry.org/psychiatrists/practice/dsm>

Recommended Drinking Limits

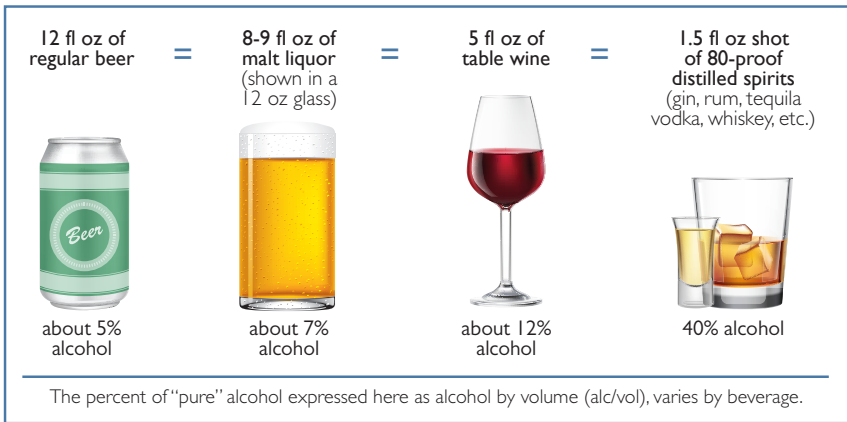
Based on the accumulated epidemiological evidence, individuals who drink beyond the following levels are at increased risk of adverse consequences of drinking (National Institute for Alcohol Abuse and Alcoholism [NIAAA]):

- An average of two drinks daily (14 drinks per week) for younger men; an average of one drink daily (seven drinks per week) for women or older male adults (≥ 65 years)
- Heavy drinking is defined as four drinks on any occasion for men; or three drinks on any occasion for women or older male adults

Definition of a standard drink: 12 g of alcohol

Roughly equivalent to:

- **Beer:** 12 fluid ounces
- **Wine:** 5 fluid ounces
- **Distilled spirits (80 proof):** 1.5 fluid ounces



Note that safe drinking limits may be substantially lower for some patients, depending on factors such as comorbidities (e.g., liver disease, HIV), pregnancy, and interacting medications.

A great number of people drink more than the recommended limits but do not meet criteria for Alcohol Use Disorder. These drinkers account for the majority of alcohol-related morbidity and mortality in the general population. All patients who misuse alcohol should receive focused medical attention and intervention.

Epidemiology

- U.S. Veterans suffering from Alcohol Use Disorder had a 2.3 times greater likelihood of death by all causes.

- 35-40% of patients with HIV in primary care settings have documented diagnoses of Alcohol Use Disorder; many more might drink above recommended levels in ways that pose health risks.
- Alcohol Use Disorder causes substantial morbidity and mortality. Medical conditions associated with alcohol misuse include alcohol withdrawal syndrome, hepatitis, cirrhosis, pancreatitis, thiamine deficiency, neuropathy, cardiomyopathy, hypertension, stroke, breast cancer, depression, and cancers of the oropharynx, larynx, and esophagus.
- Heavy drinking can increase disease progression of HIV.
- Excessive alcohol use accounts for one in 10 deaths among adults aged 20–64. A total of 30,722 people died of alcohol-induced causes in the United States in 2014.
- Alcohol use in the United States is associated with:
 - 31% of all traffic fatalities (2014)
 - 25% of emergency department trauma cases (2011)
 - 70% of water recreation deaths (2016)
 - 38,179 deaths related to chronic liver disease and cirrhosis (2014)
- Alcohol use compounds the liver damage associated with hepatitis C and hepatitis B, and accelerates progression to cirrhosis.
- Concomitant use of alcohol and hepatotoxic drugs (including some antiretrovirals (ARVs) and statins) may increase the risk of early and severe liver damage.
- The risk of pancreatitis caused by didanosine is higher among patients who use alcohol chronically.



EVALUATION



SCREENING

Alcohol Misuse Screening

At the initial visit and at least annually thereafter: Screen all patients for alcohol misuse. Ask drinkers the questions from the Alcohol Use Disorders Identification Test Consumption Questions (AUDIT-C). The AUDIT-C comprises the first three questions of the World Health Organization (WHO) AUDIT. AUDIT-C is a mandatory clinical reminder in the VA's electronic medical record.

VA recommends universal screening to identify patients who misuse alcohol. Screening followed by brief counseling interventions or treatment has been shown to decrease drinking and improve health outcomes.

- Ask all patients whether they currently drink alcohol. Ask about past alcohol use, and about family history of alcohol-related problems.

- For drinkers, use the AUDIT-C screening questionnaire (see below) to assess for risky drinking (see above for recommended drinking limits).
- Mild Alcohol Use Disorder requires two to three symptoms from a list of 11 on the DSM-5.
- Goals for evaluation:
 - Determine diagnosis specificity, treatment sensitivity, and case formulation

AUDIT-C Test

The Alcohol Use Disorders Identification Test (AUDIT-C) is an alcohol screen that can help identify patients who are hazardous drinkers or have active alcohol use disorders (including alcohol abuse or dependence).

AUDIT-C	
Q1: How often did you have a drink containing alcohol in the past year?	
Answer	Points
Never	0
Monthly or less	1
Two to four times a month	2
Two to three times a week	3
Four or more times a week	4
Q2: How many drinks did you have on a typical day when you were drinking in the past year?	
Answer	Points
None, I do not drink	0
1 or 2	0
3 or 4	1
5 or 6	2
7 to 9	3
10 or more	4
Q3: How often did you have six or more drinks on one occasion in the past year?	
Answer	Points
Never	0
Less than monthly	1
Monthly	2
Weekly	3
Daily or almost daily	4
The AUDIT-C is scored on a scale of 0-12 (scores of 0 reflect no alcohol use). In men, a score of 4 or more is considered positive; in women, a score of 3 or more is considered positive. Generally, the higher the AUDIT-C score, the more likely it is that the patient's drinking is affecting his/her health and safety.	

Note: This questionnaire (the AUDIT-C) is reprinted with permission from the World Health Organization. The Alcohol Use Disorders Identification Test is a publication of the World Health Organization.

Rx MANAGEMENT

Brief counseling with specialty referral as indicated can be effective in reducing hazardous drinking. Patients with Alcohol Use Disorders may require comprehensive treatment programs that include the services of medical providers, psychologists, and psychiatrists to assist with comorbid psychiatric conditions, social workers, housing counselors, case managers, and substance abuse counselors.

- **Short-term goals:** treating alcohol withdrawal as needed; encouraging abstinence or drinking within safe levels; encouraging participation in substance use treatment programs through the VA; engaging family and community support; ensuring adequate resources for housing, food, and income
- **Long-term goals:** sustained abstinence from alcohol use or drinking within safe levels; recovery of self-esteem, health, and social functioning

Brief interventions, delivered by a care provider in any setting, can be made using the 4 As approach: **Ask, Assess, Advise, and Assist.**

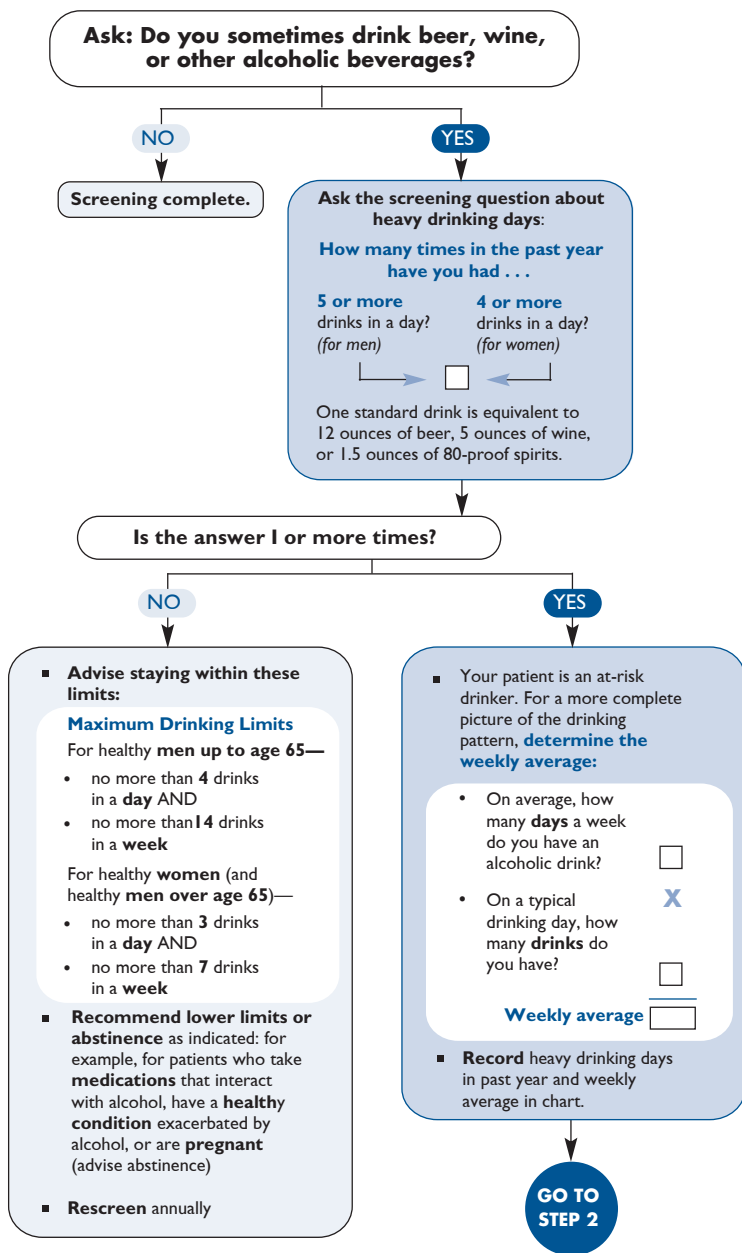
- **Ask** about alcohol use, using AUDIT-C.
- **Assess** for Alcohol Use Disorders.
- **Advise** all patients, even those with no reported heavy drinking, to stay within healthy drinking limits, keeping comorbidities in mind. Particularly for those with liver disease, there is no known safe level of alcohol consumption, and alcohol may be particularly dangerous for patients with HIV/HCV coinfection.
- **Assist** patients with brief interventions, pharmacotherapy, and referral for treatment services.
 - Brief (<5 min) alcohol intervention (BAI) can be extremely effective for alcohol misuse.
 - Key components:
 - Aim to reach agreement on a drinking goal.
 - Let the patient lead the discussion; for example, ask patients (rather than tell them) how they think alcohol use affects their health.
 - Aim for a nonjudgmental atmosphere, using open-end questions and eye contact.
 - Give choices in the discussion rather than force topics on the patient. For example, ask about stressors and how alcohol use fits in with these.
 - Remember that patients vary in their degree of readiness to change.

- Patients need to understand the importance of change, to have a sense of confidence about their ability to change, and to have a support system.
- Avoid lecturing or cheerleading; if it happens, take a step back and ask an open-end question such as “What do you think of this?”
- The Department of Veteran’s Affairs (VA) Alcohol and Drug Dependence Rehabilitation Program provides medical, social, vocational, and rehabilitation therapies to eligible alcohol and drug dependent Veterans. The programs offer various forms of treatment including detoxification, rehabilitation, and psychiatric care. Treatment programs are located in the VA medical centers and clinics.
- Patients with Alcohol Use Disorder may be offered one or more of the following interventions considering patient preference and provider training/competence:
 - Behavioral Couples Therapy for Alcohol Use Disorder
 - Cognitive Behavioral Therapy for Substance Use Disorders
 - Community Reinforcement Approach
 - Motivational Enhancement Therapy
 - 12-Step Facilitation
- Referral to 12-step programs (i.e., Alcoholics Anonymous) is helpful to many patients; AA meetings are held worldwide.
 - The Drinkers Check-up is a self-evaluation tool with information on cessation.
- Reinforce and reevaluate intervention messages at each visit.

The following is an algorithmic representation of screening and intervention using this approach from the National Institute on Alcohol Abuse and Alcoholism (NIAAA).

HOW TO SCREEN FOR HEAVY DRINKING

STEP 1 Ask About Alcohol Use



National Institute on Alcohol Abuse and Alcoholism. A Pocket Guide for Alcohol Screening and Brief Intervention. Rockville, MD: NIAAA; 2005

HOW TO ASSESS FOR ALCOHOL USE DISORDERS

STEP 2 Assess For Alcohol Use Disorders

Next, determine if there is a *maladaptive pattern of alcohol use*, causing *clinically significant impairment or distress*.

Determine whether, in the past 12 months, your patient's drinking has **repeatedly** caused or contributed to

- risk** of bodily harm (drinking and driving, operating machinery, swimming)
- relationship** trouble (family or friends)
- role failure** (interference with home, work, or school obligations)
- run-ins** with the law (arrests or other legal problems)

If yes to **one or more** → your patient has **alcohol abuse**.

In either case, proceed to assess for dependence symptoms.

Determine whether, in the past 12 months, your patient has

- not been able to cut down or stop** (repeated failed attempts)
- not been able to stick to drinking limits** (repeatedly gone over them)
- shown tolerance** (needed to drink a lot more to get the same effect)
- shown signs of withdrawal** (tremors, sweating, nausea, or insomnia when trying to quit or cut down)
- kept drinking despite problems** (recurrent physical or psychological problems)
- spent a lot of time drinking** (or anticipating or recovering from drinking)
- spent less time on other matters** (activities that had been important or pleasurable)

If yes to **three or more** → your patient has **alcohol dependence**.

Does patient meet criteria for abuse or dependence?

NO

GO TO
STEPS 3 & 4
for
AT-RISK
DRINKING

YES

GO TO
STEPS 3 & 4
for
ALCOHOL USE
DISORDERS

HOW TO CONDUCT A BRIEF INTERVENTION

FOR AT-RISK DRINKING (no abuse or dependence)

STEP 3 Advise and Assist

- **State your conclusion and recommendation clearly** and relate them to medical concerns or findings.
- **Gauge readiness to change drinking habits.**

Is patient ready to commit to change?

NO

- **Restate your concern.**
- **Encourage reflection.**
- **Address barriers to change.**
- **Reaffirm your willingness to help.**

YES

- **Help set a goal.**
- **Agree on a plan.**
- **Provide educational materials.** (See <http://www.niaaa.nih.gov/guide>.)

STEP 4 At Followup: Continue Support

REMINDER: Document alcohol use and review goals at each visit.

Was patient able to meet and sustain drinking goal?

NO

- **Acknowledge that change is difficult.**
- **Support positive change** and address barriers.
- **Renegotiate goal and plan;** consider a trial of abstinence.
- **Consider engaging significant others.**
- **Reassess diagnosis** if patient is unable to either cut down or abstain.

YES

- **Reinforce and support continued adherence** to recommendations.
- **Renegotiate drinking goals** as indicated (e.g., if the medical condition changes or if an abstaining patient wishes to resume drinking).
- **Encourage to return** if unable to maintain adherence.
- **Rescreen** at least annually.

National Institute on Alcohol Abuse and Alcoholism. A Pocket Guide for Alcohol Screening and Brief Intervention. Rockville, MD: NIAAA; 2005

HOW TO CONDUCT A BRIEF INTERVENTION

FOR ALCOHOL USE DISORDERS (abuse or dependence)

STEP 3 Advise and Assist

- **State your conclusion and recommendation clearly** and relate them to medical concerns or findings.
- **Negotiate a drinking goal.**
- **Consider evaluation by an addiction specialist.**
- **Consider recommending a mutual help group.**
- For patients who have dependence, **consider**
 - the need for **medically managed withdrawal** (detoxification) and treat accordingly.
 - prescribing a **medication** for alcohol dependence for patients who endorse abstinence as a goal.
- **Arrange followup appointments**, including medication management support if needed.

STEP 4 At Followup: Continue Support

REMINDER: Document alcohol use and review goals at each visit.

Was patient able to meet and sustain drinking goal?

NO

- **Acknowledge that change is difficult.**
- **Support efforts** to cut down or abstain.
- **Relate drinking to ongoing problems** as appropriate.
- **Consider** (if not yet done):
 - consulting with an **addiction specialist**.
 - recommending a **mutual help group**.
 - engaging **significant others**.
 - prescribing a **medication** for alcohol-dependent patients who endorse abstinence as a goal.
- **Address coexisting disorders**—medical and psychiatric—as needed.

YES

- **Reinforce and support continued adherence.**
- **Coordinate care** with specialists as appropriate.
- **Maintain medications** for alcohol dependence for at least 3 months and as clinically indicated thereafter.
- **Treat coexisting nicotine dependence.**
- **Address coexisting disorders**—medical and psychiatric—as needed.

National Institute on Alcohol Abuse and Alcoholism. A Pocket Guide for Alcohol Screening and Brief Intervention. Rockville, MD: NIAAA; 2005



WHEN TO REFER

Most patients with moderate or severe alcohol misuse should be referred to specialized Alcohol or Substance Use Disorder treatment services. Patients with comorbid conditions that are adversely affected by alcohol, such as HIV, HCV, liver disease, or depression, may need treatment even if they do not meet typical criteria for Alcohol Use Disorders.

Patients in withdrawal (tremors, sweats, anxiety, disorientation, or visual, auditory, or tactile hallucinations) should be referred to an emergency department for immediate evaluation and treatment, and should be referred to a detoxification program if available.

Pharmacotherapy for Relapse Prevention

Although pharmacotherapy may help to prevent relapse, multimodal treatment that includes medical therapy with or without behavioral therapy may be more effective.

Note: Although it is expected that the efficacy of these medications will be similar in patients with and without HIV infection, increased monitoring for adverse effects should be exercised.

A randomized controlled trial involving patients who are HIV-uninfected compared various combinations of medical management, medication, and behavioral therapy for treatment of alcohol dependence in recently abstinent patients. The study showed that:

- All treatment groups had substantial increases in the percentage of days abstinent from alcohol.
 - The highest percentage of days abstinent (77-80%) was seen in three treatment groups: patients who received naltrexone (100 mg QD) + medical management (nine sessions with a health care professional), naltrexone + medical management + a combined behavioral intervention (CBI) (20 sessions), or medical management + CBI + placebo pills.
 - Patients who received CBI alone (no medical management or pills [whether placebo or naltrexone]) had the lowest abstinence rates.
 - Acamprosate was no more effective than placebo.
 - Treatment effects largely dissipated after 1 year; thus ongoing monitoring is important, and treatment of relapse may be necessary.

Table I. Pharmacotherapy for Relapse Prevention

Medication	Standard Dosage	Comments
<p>Naltrexone (oral: Depade®, ReVia®)</p>	<p>50-100 mg QD for ≥ 3 months</p> <ul style="list-style-type: none"> • Start upon cessation of alcohol use. • Optimal duration of therapy not known; most study subjects treated for 3-4 months; treatment effects tend to wane after therapy is stopped. 	<ul style="list-style-type: none"> • Pure opioid receptor antagonist • Avoid in patients who use opioids (precipitates withdrawal symptoms). • Avoid in patients with acute hepatitis or liver failure. • Possible adverse effects: depression, nausea, cramping, vomiting, headache, joint or muscle pain, hepatotoxicity, injection site reactions, unusual tiredness • Check LFTs before and after treatment.
<p>Naltrexone (IM: Vivitrol®)</p>	<p>190-380 mg IM monthly for ≥ 3 months</p> <ul style="list-style-type: none"> • Start upon or just after cessation of alcohol use; greater benefit may be seen in patients who achieve some duration of alcohol abstinence (e.g., 2-4 days) before the initial injection of naltrexone. • Useful for patients with adherence issues. See the VA PBM Clinical Guidance Criteria for Use website, http://www.pbm.va.gov/clinicalguidance/criteriaforuse.asp. 	<ul style="list-style-type: none"> • Pure opioid receptor antagonist • Possible adverse effects: depression, nausea, cramping, vomiting, headache, joint or muscle pain, hepatotoxicity, injection site reactions, unusual tiredness • Avoid in patients who use opioids (precipitates withdrawal symptoms). • Avoid in patients with acute hepatitis or liver failure. • 380 mg dose has been standard but does not confer more abstinence advantage and causes more side effects.
<p>Disulfiram (Antabuse®)</p>	<p>250-500 mg QD as adjunct during outpatient treatment period</p> <ul style="list-style-type: none"> • Start ≥ 12 hours after last alcohol consumption. • Classed as a latency-reversing agent. 	<ul style="list-style-type: none"> • Disulfiram acts as an acetaldehyde dehydrogenase inhibitor. • Concurrent alcohol consumption increases plasma acetaldehyde concentra-

Medication	Standard Dosage	Comments
-	<ul style="list-style-type: none"> • Therapy should be reevaluated at six weeks to six months. 	<p>tions 5-10 times, causing flushing, headache, sweating, tachycardia, hypotension, nausea, vomiting, vertigo, and anxiety within 15 minutes.</p> <ul style="list-style-type: none"> • Other possible adverse effects include delirium, hepatotoxicity (monitor LFTs before treatment and every 3 months during treatment), neuropathy. • Do not administer to patients who take ARV syrups or other medications that contain alcohol or propylene glycol (e.g., RTV, LPV/r, and FPV liquid formulations). • Patients must avoid OTC medications containing alcohol (e.g., cough syrup), as well as sauces, vinegars, and foods containing alcohol. • Multiple other drug interactions, including with phenytoin, rifampin, isoniazid, and warfarin • Disulfiram may increase etravirine levels.
Acamprosate (Campral®)	<p>666 mg TID for three months</p> <ul style="list-style-type: none"> • Should only be used in patients with at least four days of abstinence and only mild withdrawal symptoms who are in a comprehensive management program including appropriate behavioral interventions. • Start as soon as possible after abstinence is established and continue through relapses. • Adjust dosage for renal failure: <ul style="list-style-type: none"> • Creatinine clearance (CrCl) 30-50 mL/min: 333 mg TID • CrCl ≤30 mL/min: contraindicated 	<ul style="list-style-type: none"> • GABA analogue; decreases excitatory glutamergic neurotransmission during withdrawal. • Patients should be closely monitored for depression or suicidal thinking. • Other possible adverse effects: dizziness, diarrhea, somnolence. • COMBINE study did not show that acamprosate was more effective than placebo.

HIV Protease Inhibitors Used in Combination with Other Pharmacotherapy	Comments
Ritonavir capsules, oral solution Lopinavir/ritonavir oral solution Tipranavir, oral capsules	<ul style="list-style-type: none"> • These medications contain alcohol and may precipitate reactions. • Contraindicated in severe hepatic dysfunction: transaminases >3x upper level of normal.



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Substance Use

KEY POINTS

- Substance use is a significant cause of morbidity and mortality in itself, and can increase a person's risk of HIV transmission and acquisition.
- Ask all patients about any current or recent use of drugs or alcohol, or misuse of prescription drugs. Ask specifically about injection drugs, opioids (prescription and non-prescription), methamphetamine, cocaine, and “club drugs.”
- For patients who are using substances, check in at each visit by asking directly about substance use. The Center for Substance Abuse Treatment recommends asking patients their perceptions of the **importance** of the issue and their **confidence** in making any kind of change.
- Comprehensive Substance Use Disorder (SUD) treatment programs are available in VA, which may provide a range of treatment options from individual therapy, group therapy, pharmacotherapy, partial day programs. Some VA facilities offer inpatient rehabilitation services.
- Non-SUD medical providers may be able to offer medication assisted therapy (MAT) for addiction therapy with specialized certification, <https://findtreatment.samhsa.gov/>.
- Treatment for substance use disorders (SUDs) can be an effective intervention for HIV prevention.
- Treatment options exist along a continuum and include recovery and recovery support, medication assisted treatment (MAT), detoxification, individual and group therapy, treatment of comorbid conditions, maintenance of treatment, and prevention of relapse.
- Comprehensive SUD treatment may reduce drug abuse by 40-60%, reduce associated crime by 40-60%, and increase employment prospects by 40%.
- VA embraces a recovery model for addictions defined by Substance Abuse and Mental Health Services Administration's (SAMHSA) in which recovery is built on access to evidence-based clinical treatment and recovery support services, enhancing a person's whole health, life meaning, purpose and stability. See SAMHSA website for more information, <https://www.samhsa.gov/recovery>.
- Brief interventions for SUDs can be helpful in non-SUD specialty clinical settings.



BACKGROUND

- Substance abuse has been linked to increased HIV transmission, delayed diagnosis, delayed initiation and poor adherence to therapy, and challenges in engagement in care.
- Substances frequently abused in the United States include alcohol, nicotine, cannabis, prescription medications (opioids, narcotics, sedatives, and many others), cocaine, heroin, methamphetamines, tranquilizers, hallucinogens, anabolic steroids, inhalants, and club drugs.

Note: Some medications mentioned in this chapter may not be available on the VHA National Formulary (<https://www.pbm.va.gov/NationalFormulary.asp>). Consult VA pharmacists for alternatives.

- Club drugs can include methylenedioxymethamphetamine (MDMA, or ecstasy), flunitrazepam (Rohypnol), gamma-hydroxybutyrate (GHB), ketamine, and inhaled nitrates (poppers).

- Comorbidities are common: problematic alcohol use, tuberculosis, HIV, hepatitis C, hepatitis B, sexually transmitted infections (STIs), mental health disorders, and homelessness, to name a few.
- People who abuse drugs are at high risk of unsafe sex practices. For example, cocaine, methamphetamine, and other stimulant abusers are more likely to involve themselves in prostitution and unsafe sex in order to obtain money for drugs. Methamphetamines are a very big problem in some areas.
- The focus of this chapter is on the recognition and management of opioids abuse (prescription and bought on the street) heroin, and methamphetamines. These drugs are a primary priority for VA. Abuse of cocaine, cannabis, and club drugs will be addressed briefly.
- Alcohol misuse and tobacco use are discussed in separate chapters. See **Alcohol Use**, p. 91; and **Tobacco Use**, p. 127.

Veterans with HIV*	
Alcohol use disorder	34%
Cannabis use	17%
Cocaine use	25%
Opioid use	11%
Other/Unspecified drug use	24%
Tobacco use	47%

*Veterans with HIV in VA care in 2016 who ever had a VA diagnosis of selected comorbid conditions prior to or during the target calendar year.

Definitions

Addiction: a primary, chronic, neurobiologic disease, with genetic, psychosocial, and environmental factors influencing its development and manifestations. It is characterized by behaviors that include one or more of the following: impaired control over substance use, compulsive use, continued use despite harm, and craving.

Intravenous drug use (IDU): includes IV drug use, intramuscular (IM) drug use, and skin popping. IDU can involve opiates, methamphetamines, cocaine, sedatives/tranquilizers, or other drugs.

Physical dependence: a state of adaptation that is manifested by a drug class-specific withdrawal syndrome that can be produced by abrupt cessation, rapid dose reduction, decreasing blood level of the drug, or administration of an antagonist.

Recovery: Substance Abuse and Mental Health Services Administration's (SAMHSA) defines recovery as a "process of change through which individuals improve their health and wellness, live self-directed lives, and strive to reach

their full potential. Recovery is built on access to evidence-based clinical treatment and recovery support services for all populations.”

Severity of Substance Use Disorders: symptoms indicate the severity from mild to severe:

- mild – 2-3 symptoms
- moderate – 4-5 symptoms
- severe – 6 or more symptoms

Substance abuse: a maladaptive pattern of substance use that has become socially, legally, or occupationally problematic for an individual.

Substance dependence: a maladaptive pattern of substance use, leading to clinically significant impairment or distress, manifested as tolerance (need for increased amounts of the substance or decreased effect with the same amount) or withdrawal symptoms.

Substance Use Disorder (SUD): Classified by the DSM-5 as mild, moderate, or severe depending on the number of symptoms present out of the 11 criteria listed below:

1. Taking the substance in larger amounts or for longer than you're meant to.
2. Wanting to cut down or stop using the substance but not managing to.
3. Spending a lot of time getting, using, or recovering from use of the substance.
4. Cravings and urges to use the substance.
5. Not managing to do what you should at work, home, or school because of substance use.
6. Continuing to use, even when it causes problems in relationships.
7. Giving up important social, occupational, or recreational activities because of substance use.
8. Using substances again and again, even when it puts you in danger.
9. Continuing to use, even when you know you have a physical or psychological problem that could have been caused or made worse by the substance.
10. Needing more of the substance to get the effect you want (tolerance).
11. Development of withdrawal symptoms, which can be relieved by taking more of the substance. See <https://www.buppractice.com>. Note: Registration Login required.

Tolerance: a state of adaptation in which exposure to a drug induces changes that result in a diminution of one or more of the drug's effects over time.

Epidemiology

- Drug abuse is closely associated with HIV infection in the United States.

- In 2015, 6% of the nearly four thousand diagnoses of HIV in the United States were attributed to IDU.
- The National Institute on Drug Abuse (NIDA) shows the number of people who admit to ever using an illicit drug rose from 31.3% in 1979 to 48.8% in 2015. Annual overdose deaths rose from 17,415 in 2000 to 52,404 in 2015.
- In 2015, two million Americans had a substance use disorder involving prescription pain relievers, tranquilizers, stimulants, and sedatives; and 591,000 had a substance use disorder involving heroin.
- It is estimated that 23% of heroin users will develop an opioid addiction.
- The National Survey on Drug Use and Health (NSDUH) reports that cocaine users number 1.5 million, or 0.6% of the population.
- Marijuana is a commonly used drug, which is now legal in many states. The National Institute of Health (NIH) reports nearly six million people had a marijuana use disorder in 2015, with the amount of THC increasing steadily over the past few decades.
- Men are more likely than women to use almost all types of substances.

Substance Abuse, HIV Infection, and ARV Therapy

- Cocaine use decreases CD4 cell production by as much as 3- to 4-fold and increases the rate of HIV viral replication by up to 20-fold.
- In a prospective cohort study, active drug use was strongly associated with underutilization of ARV therapy, nonadherence, and inferior virologic and immunologic responses to ARV therapy, compared with former drug use and nonuse of drugs.
- Methamphetamine and cocaine binges are associated with interruptions in ARV therapy adherence.
- Primary providers for patients with HIV may be less likely to prescribe ARVs to their IDU patients even when the patients meet criteria for starting ARV therapy if the physicians have negative attitudes toward treating IDU. To improve quality of care, providers must be able to assess complex symptoms and have adequate time with patients.



EVALUATION

There are many reasons to identify patients who abuse substances, and to try motivating them toward treatment. Unlike the strong evidence on effectiveness of brief interventions for alcohol misuse, there is less data on brief interventions in primary care settings for other substances (TIP 34). Approaches that focus on the effects of substance abuse on the patient's own health (e.g., poor ARV therapy adherence, acquisition of opportunistic and other infections) may be useful

and Medication-Assisted Treatment (MAT) can be a critically important intervention. See below; and **Prevention of HIV Transmission with Positives**, p. 45.

Note on Pre-exposure Prophylaxis (PrEP) for HIV Prevention

If appropriate providers should talk to their patients who are HIV-positive about whether PrEP may be an option for any sexual or drug using partners who are HIV-negative. If so, see **PrEP for Sexual and Drug Partners**, p. 81. Note that VA can only provide care for Veterans enrolled in VA care, so any non-enrolled sexual or drug using partners who are HIV-negative should be referred to PrEP providers in the community.

Brief Interventions for Patients Identified with SUD

- It can be helpful for providers to begin conversations about substance use at each visit.
- Some patients may not be ready to engage in SUD treatment, so enhancement of motivation can be helpful.
- Recovery and recovery support is flexible to ensure cultural relevancy for each individual. Veterans' needs. Cultural backgrounds vary and so must their treatments.
- It is helpful for providers to keep overall patient goals in mind: Return to productive functioning, increased health, stability in housing, building purpose, meaning, and community through recovery support.
- Building meaningful relationships with your patients that supports recovery through reduced stigma and judgment of behaviors, and increases a patient's motivation in addressing substance use and incorporate recovery oriented principles in their daily lives can also be an important brief intervention.

Raise Importance

Ask: "On a scale of 1-10, how **important** is it for you to change your substance use?"

"Why did you give it (number) and not a (lower number)?"

"What would it take for you to give it a (higher number)?"

Raise Confidence

Ask: "On a scale of 1-10, how **confident** are you that you can change successfully?"

"Why did you give it (number) and not a (lower number)?"

“What would it take for you to give it a (higher number)?”

A useful technique for facilitating a patient-centered conversation about the readiness to change is to ask questions about the patient’s perception of **importance** of the issue and his or her **confidence** in making any kind of change.

VA provides many Motivational Interviewing (MI) and Motivational Enhancement Therapy (MET) trainings. MI and MET are brief, well researched treatments used to determine one’s motivation and readiness to change. The goal is to support Veterans with acceptance and compassion as they undertake changing their lives. Visit <https://www.mentalhealth.va.gov/> for more information.

Management of Specific Substance Use Disorders

VA has extensive resources for the management of SUDs. Visit <https://www.pbm.va.gov/>.

Heroin and Other Opioids

Behavioral Interventions

- In addition to brief primary care provider interventions suggested above, **refer for specialty evaluation and treatment within VA**, or to substance abuse counselors in community-based organizations, rehabilitation facilities, and methadone maintenance sites.
- It is important to begin conversations with patients about their substance abuse. However, specific psychosocial interventions for opioid use have yet to demonstrate consistent efficacy.
- If the patient is in withdrawal, or at high risk of withdrawal, refer for detoxification or to the emergency department. If unstable (medically or psychiatrically), refer to the emergency department.
- For local (non-VA) substance abuse resources: 800-662-HELP.
- Narcotics Anonymous provides group support.
- Counsel on safe injection practices and needle exchange options where available, to reduce the risk of transmission of HIV, hepatitis C, and other bloodborne pathogens.
- The American Academy of Pain Medicine recommends a written treatment agreement or contract signed by the provider and patient at the time of starting pharmacological therapy for pain.

Pharmacologic Interventions

- Treat comorbid psychiatric conditions.
- Opioid agonist therapy is the gold standard for heroin addiction treatment.
- **Methadone** is a full opioid agonist used for opioid agonist therapy in opioid treatment programs.
- Methadone maintenance programs typically start with a dose of ≤ 30 mg and adjust to the lowest effective dose that suppresses withdrawal signs and symptoms. Typical dosage is between 60 mg and 120 mg once a day (QD).

- Adverse effects include constipation, weight gain, drowsiness, excessive sweating, and changes in libido, and risk of overdose (accidental or deliberate).
- Can increase QT-interval, precipitating torsade de pointes and other arrhythmias. Should be avoided in patients with baseline prolonged QTc; use with caution if coadministering other medications that prolong QT.
- Methadone levels may be lowered by various ARVs. See **Potential ARV Interactions**, below; and **Common Medications**, p. 11.
- **Suboxone** is a combination of buprenorphine and naloxone. Buprenorphine is an opioid medication. Naloxone blocks the effects of opioids.
- **Naloxone** is a highly effective intervention for reversing opioid overdoses.
- **Buprenorphine** is a partial μ -opioid agonist and weak kappa antagonist with 25-50 times the analgesic potency of morphine. It has a pharmacologic ceiling, and a lower risk of overdose and abuse than full opioid agonists.
- By federal regulation and VA policy; physicians are able to prescribe buprenorphine only with eight hours or more of special training and a specific DEA certificate.
- It is administered sublingually, in tablet or film formulation.
- Buprenorphine Transdermal System (BTDS) is a patch with a dose of one 20 mcg/hour. BTDS should not be exceeded because of the risk of QT-prolongation.
- At high dosages, it may block the effects of full opioid agonists, leading to withdrawal. Therefore, patients should stop taking short-acting opioids 12-24 hours before starting buprenorphine and reduce their methadone use to a maximum of 30-40 mg/day.
- In the United States, buprenorphine is most commonly co-formulated with naloxone. Naloxone is poorly absorbed sublingually; however, if the tablet is crushed and injected parenterally, the naloxone precipitates opiate withdrawal.
- Buprenorphine has been approved for use in office-based opioid dependence treatment outside regulated Opioid Treatment Programs.
- Buprenorphine is induced with an initial daily dosage of 2-8 mg and is increased by 2-4 mg QD until relief from withdrawal symptoms is achieved. The usual dosage is 12-16 mg QD; maximum recommended dosage is 32 mg QD.
- Side effects include depression, disturbed sleep, drowsiness, sweating, headaches, nausea, constipation, and reduced libido. Mild increases in alanine aminotransferase (ALT) have been reported. Respiratory depression may occur, especially if misused intravenously.
- Buprenorphine may interact with protease inhibitors (PIs) and with Efavirenz (EFV). See **Potential ARV Interactions**, below.
- In acute pain episodes, buprenorphine can be used every eight hours for analgesic effects.
- **Naltrexone**: opioid antagonist. Precipitates opiate withdrawal; appropriate only for patients with >7 days of abstinence.
- May be a useful adjuvant to psychosocial therapy (though data are limited).
- Compliance has been poor with the oral tablets; an extended-release formulation has better compliance and is FDA approved but does not yet have Pharmacy Benefits criteria for use in VA.

- Consider oral naltrexone as a component of a substance abuse program for highly motivated patients (e.g., those who face severe consequences for relapse, such as health care professionals and parolees).

Methamphetamines and Cocaine

Behavioral Interventions

- If unstable (medically or psychiatrically), refer to the emergency department or hospitalize.
- Behavioral interventions are the mainstay of treatment; no pharmacologic agents have proven efficacy. Computer-based text messaging Interventions and mobile apps are under study.
- Refer to outpatient or inpatient behavioral counseling: including motivational interviewing and cognitive-based therapy (e.g., Matrix Model or Goal Management Training), contingency management to reward early abstinence.
- Refer to harm reduction programs and cognitive-behavioral therapy tailored to substance abusers.
- For local (non-VA) substance abuse resources: 800-662-HELP.
- Narcotics Anonymous provides methamphetamine- and cocaine-specific groups.
- Crystal Meth Anonymous offers fellowship in many states.
- Ask about ARV therapy adherence at each visit, as methamphetamine users frequently go on binges that lead to interruptions in ARV therapy adherence.
- Methamphetamine use is associated with unsafe sexual behaviors. Explore risk behaviors, screen for STDs, and counsel on safer sex options. See **Prevention of HIV Transmission with Positives**, p. 45.
- Provide written or illustrated instructions that can be processed visually, as methamphetamine users often have impaired auditory memory.

Pharmacologic Interventions

- For treatment of acute methamphetamine withdrawal, no medication has proven to be effective.
- No medication has been FDA approved for the treatment of cocaine addiction. Systematic reviews of antidepressants, dopamine agonists, anticonvulsants, and antipsychotics have not shown consistent efficacy.
- Treat comorbid psychiatric conditions.
- Antidepressants have not been shown to improve long-term treatment outcomes.
- Dextroamphetamine replacement therapy has not shown greater efficacy than placebo. Studies of other treatments are ongoing.
- Ritonavir (RTV) inhibits amphetamine metabolism and can lead to a 2- to 3-fold increase in amphetamine levels. Patients should be educated about this interaction.
- Disulfiram, amantadine, tiagabine, topiramate, and baclofen have been reported to be of possible benefit in cocaine addiction.
- Peer support groups such as Cocaine Anonymous can improve outcomes.

Addiction Pharmacotherapy

Medication assisted therapy (MAT) for opioid use disorder (OUD) offers several options which can be chosen based on the risks and benefits for the patient. Pharmacotherapy is most effective when provided in combination psychosocial support. Currently, there are three FDA approved medications for OUD: methadone, buprenorphine and naltrexone. Methadone is a synthetic mu-opioid receptor full agonist. It has been shown to be effective in treating opioid and heroin use disorder, decreasing mortality, reducing HIV risk by reducing IV drug use and improving health outcomes. Methadone can have additional benefit in treatment of chronic pain and high level of cravings. Methadone use for addiction is administered once daily; where methadone use for pain treatment is usually given 2-3 times daily.

Treatment centers for methadone often provide observed administration, improving adherence and reducing the risk of misuse or diversion. Such programs may offer psychotherapy with counselors and in group settings, which can be advantageous to those users who need additional support. After time, patients who are stable may be allowed to take methadone home to self-administer between visits.

Methadone carries the risk of drug-drug interactions as it is hepatically metabolized through the cytochrome P450 enzyme 3A4, and QT-interval prolongation must be monitored. Other important side effects include respiratory depression, which is especially dangerous for patients on benzodiazepines, concurrent use of alcohol or other opioid substances. If opioids are used for chronic pain, they may also have short acting agent.

Buprenorphine is a partial mu-opioid receptor agonist with some antagonist properties. It is prescribed from an outpatient office setting, giving patients flexibility compared to the observed therapy from a methadone program. However, there is an increased risk of diversion through selling or injection intravenously; 10 times more so than methadone, according to a Winstock study.

Naloxone is incorporated into some buprenorphine products to minimize this abuse potential. Buprenorphine has less risk of respiratory and CNS depression although patients must still be advised of the risk. Caution is needed during induction as it may induce withdrawal for those who are not already in mild to moderate withdrawal. It has fewer drug-drug interactions than methadone. Naltrexone is a mu-opioid antagonist which comes in both daily pill formulation and monthly depot injection. As an opioid antagonist, there is minimal to no potential for abuse and diversion.

Naltrexone is useful for those who are also diagnosed with alcohol use disorder (AUD), as it is FDA-indicated for both. Further, for those in treatment programs with a requirement to be opioid-free, this is an effective medication. Naltrexone has a higher risk of hepatic toxicity than opioid agonist medications and requires monitoring of liver enzymes. Methadone is extensively metabolized through the

liver and impairment can possibly lead to accumulation and increased risk for CNS toxicity. As a result, naltrexone should not be given to those with significant liver cirrhosis or dysfunction. The monthly injection formulation increases adherence by decreasing the number of administrations. It is on the national formulary, but locally may be restricted also due to the cost of IM-naltrexone. Naltrexone depot formulation carries the same risks as the by-mouth daily pill.

Turncliff et al., evaluated long acting naltrexone in patients with mild-moderate liver disease. The injection avoids extensive first-pass elimination, and can reduce hepatotoxicity risk vs. oral formulation. Naltrexone should be avoided with Child-Pugh C.

For alcohol use disorder (AUD), there are currently three FDA approved medications: naltrexone, disulfiram and acamprosate. It is important to note that none of these medications will assist with alcohol withdrawal, so withdrawal must be managed prior to starting any of these options. Naltrexone is taken once daily and is effective for AUD and should be started upon alcohol cessation for management of cravings.

Naltrexone can also be initiated in patients who are actively drinking, and has been shown to help reduce episodes of heavy drinking. Chronic alcohol users with severe liver damage or cirrhosis may consider other pharmacological options as they will be at increased risk of toxicity with naltrexone. Disulfiram is an aldehyde dehydrogenase inhibitor, which stops breakdown of alcohol in the liver. This leads to uncomfortable build-up of aldehyde, causing nausea, vomiting, flushing, tachycardia, hypotension and dizziness, deterring the user from further alcohol consumption.

Disulfiram should be carefully considered as there is risk for significant toxicity. Patients need to avoid foods, drinks, topical products, or over the counter medications that contain alcohol. Disulfiram can also interact with topical products containing alcohol including hand sanitizer and other gel formulated products. As it might not present as disulfiram reaction, we have seen patients report of nausea and sometimes vomiting when taken concurrently. For example: Couple patients in SUD clinic were presenting with chronic nausea, one was found to regularly use hand sanitizer during work as a health care professional, and another was using deodorant and hair gel products that contained a small percent of alcohol.

Disulfiram is helpful in conjunction with therapy and is administered daily. However, those who choose to drink can simply not take their dose for the day and not have these effects. Patients must be adherent and committed to treatment. Acamprosate may act by normalizing central glutamatergic dysregulation in AUD, and has been shown to decrease alcohol consumption, and improve abstinence. It is thought to work on glutamate and gaba neurotransmitters in the brain. Acamprosate is taken three times daily, and is recommended to initiate after four days of sobriety. It is well tolerated with the main side effect of diarrhea. It is renally excreted, and therefore safer for those with liver disease. Those with

kidney disease are less favorable candidates. It has few drug-drug interactions and has been shown to be as effective as naltrexone in different ways. Acamprosate is better at improving abstinence, ideally initiated after cessation of alcohol. Naltrexone is better at reducing heavy drinking in addition to promoting abstinence. Naltrexone is one pill once daily, where acamprosate is two pills three times daily, which may be a factor in selecting one agent over the other.

Potential ARV Interactions

Methadone
<ul style="list-style-type: none"> • The following may decrease (↓) methadone levels. Monitor for signs of opiate withdrawal. Dosage adjustment of methadone may be needed. <ul style="list-style-type: none"> • NRTIs: ABC • NNRTIs: EFV, NVP, RPV • PIs: ATV, DRV, FPV/r, LPV/r, NFV, SQV/r, TPV/r • DLV may ↑ methadone levels. Start methadone at low dosage, monitor for methadone toxicity. • Methadone may ↓ ddl levels. Dosage adjustment not established.
Buprenorphine
<ul style="list-style-type: none"> • PIs: May ↑ buprenorphine levels and ↑ risk of adverse effects. • EFV: May ↓ buprenorphine levels; monitor for signs of opiate withdrawal. • Dosage adjustment of buprenorphine may be needed; monitor for signs of buprenorphine intoxication or withdrawal, and titrate as needed.
Ketamine
<ul style="list-style-type: none"> • PIs: May ↑ and prolong ketamine effects (↑ sedation, ↑ heart rate and blood pressure).
Cannabis/Marijuana, Ecstasy/MDMA, Amphetamines, Benzodiazepines, GHB
<ul style="list-style-type: none"> • PIs may ↑ these drug levels; patients should be warned of potential increased risk of toxicity and avoid or reduce doses.

Club Drugs and Cannabis

The effects of club drugs are less well-characterized. Here is an overview of the effects of cannabis and some common club drugs:

Club Drugs
<p>Behavioral Interventions</p> <ul style="list-style-type: none"> • Refer to cognitive behavioral therapy tailored to substance abusers. • For local substance abuse resources: 800-662-HELP.

- Narcotics Anonymous also provides group support for club drug users.

Pharmacologic Interventions

- Naloxone is a highly effective intervention for reversing opioid overdoses.
- Treat comorbid psychiatric conditions.
- RTV increases MDMA levels 5- to 10-fold and can increase the risk of fatal heat-stroke and dehydration.
- RTV also increases GHB levels, leading to increased risk of seizures, respiratory depression, and loss of consciousness.

Cannabis (Marijuana)

Also known as chronic, pot, weed, grass, Mary Jane, spliff, ganja, hash, skunk, puff, herb, and many other names

Effects

Intoxicant, stimulant, psychedelic (mild hallucinogenic), relaxant

Impact

- Both physical and psychological dependence are possible. A chronic heavy user can appear apathetic and unmotivated, and may perform poorly at work or school.
- Other health risks include those associated with impaired judgment and coordination, increased incidence of respiratory infections, as well as toxicities from adulterants (e.g., formaldehyde).
- **Note:** Veterans who receive their care from VA and who have a desire to participate in one of several State marijuana programs might ask their VA physicians to complete State authorization forms. It is VA policy to prohibit VA providers from completing forms seeking recommendations or opinions regarding a Veteran's participation in a State marijuana program. For patients who do participate in a marijuana program, VA providers should assess for misuse, adverse effects, and withdrawal. While patients participating in State marijuana programs must not be denied VA services, the decisions to modify treatment plans in those situations need to be made by individual providers in partnership with their patients.

MDMA

Also known as "ecstasy", E, X, XTC, rolls, beans, Adam

Effects

Stimulant, hallucinogenic amphetamine

Impact

- MDMA is one of the most popular recreational psychoactive drugs, most commonly sold in the form of ecstasy tablets. It is known for its empathogenic, euphoric, and stimulant effects.

- Physical effects are similar to those of amphetamines.
- Between 300 and 400 deaths have been reported from MDMA use and overheating
- Concurrent use with amphetamines, cocaine, or alcohol increases the risk of overheating.
- RTV increases MDMA levels 5- to 10-fold and can increase the risk of fatal heat stroke and dehydration.

Flunitrazepam (Rohypnol)

Also known as roofies, “date-rape” drug

Effects

Benzodiazepine sedative-hypnotic

Impact

- Flunitrazepam has been used in many date rapes in the United States, with cases also reported in Europe and Australia.
- Causes paralysis, unconsciousness, and short-term amnesia.
- Onset occurs within 10 minutes after being taken; the effects peak in 8 hours and last 12 hours.
- Mixing with alcohol at higher doses can lead to unconsciousness for several days.

Gamma hydroxybutyrate (GHB)

Also known as liquid ecstasy, GBL (a prodrug), BDO, GBH, Blue Nitro, Midnight Blue, RenewTrient, Reviarent, SomatoPro, Serenity, Enliven

Effects

Sedative depressant, anesthetic

Impact

- GHB is popular on the rave scene. It has effects of alcohol-like intoxication and sexual disinhibition.
- Higher doses can lead to disorientation, blurred vision, nausea, vomiting, impaired physical coordination, and muscle spasms.
- Onset occurs within minutes; overdose can lead to unconsciousness within 30 minutes. The risk of coma and death is potentiated by concurrent alcohol use.
- RTV increases GHB levels, leading to increased risk of seizures, respiratory depression, and loss of consciousness.

Ketamine Hydrochloride

Also known as K, Special K, Dorothy, cat tranquilizer, tekno, green

Effects

Dissociative anesthetic, hallucinogenic (same class as phencyclidine, or PCP)

Impact

- Ketamine was developed as a veterinary and human anesthetic, but it has become popular in club and rave scenes.
- Initial effects are of stimulation and euphoria, followed by sedation and hallucination (out-of-body sensations). Physical effects include nausea and vomiting, slurred speech, lack of coordination, and numbness.
- Physical risks include injury resulting from the anesthetic effects. Overdoses can lead to respiratory compromise.
- Used chronically, ketamine can increase the risk of drug-induced hepatitis.

Pain Management in Patients with SUD

Pain management should be in accordance with the principles of the VA's stepped care model for management of pain across the continuum of care, from acute to chronic.

- The prevalence of self-reported pain among patients infected with HIV ranges from 28-97%.
- Patients infected with HIV with SUD are more likely to be untreated or undertreated for pain.
- Pain management in patients with SUD may be complicated by opiate tolerance.
- Clinician concerns about pain management in patients with SUD include:
 - Drug seeking by patients
 - Diversion
 - Relapse to substance abuse
 - Legal repercussions
 - Inadequate knowledge or skills on the part of the clinician
 - Unavailability of specialists
- Patients with SUD may be concerned about pain management including:
 - Relapse to substance abuse
 - Anticipated physical discomforts (e.g., thinking that medicines will be injected; fearing side effects)
 - Fearing accusations of malingering
 - Perceived weakness in taking medications for pain
- Appropriate evaluation of pain in the patients infected with HIV and SUD includes:
 - An accurate and complete pain history, including results of previous evaluations; distinguishing between neuropathic and non-neuropathic pain may help guide therapy
 - Use of a numeric pain scale to assess and follow severity and response to therapy

- Appropriate and complete evaluation to identify correctable causes of pain (e.g., use of a neurotoxic medication in a patient complaining of painful neuropathy)
- Accurate and complete documentation of findings via computerized patient record system (CPRS)
- Principles of pain management in the patient with HIV infection and with SUD include:
 - Consider non-medication based pain management which includes pain-psychotherapy, physical therapy, and non-opioid pain management
 - Having a single provider prescribe all pain medications
 - Accurate and complete documentation of the rationale for the treatment used, including dosage, dose interval, amount prescribed, and refill procedures
 - Comply with state prescription drug monitoring programs (PDMP) guidelines
 - If a patient has an active SUD, consultation with or referral to a treatment program
 - Agreement with the patient on goals of therapy:
 - In cases of acute pain, elimination of pain is a reasonable goal, with agreement on when the need for therapy will end
 - For chronic pain, the goal should be reasonable relief of pain with a maximum level of functioning
 - Use of specific rules (contract) that addresses reports of lost medications, missed appointments etc., to promote accountability and decrease the risk of diversion or drug-seeking behavior. Visit the American Academy of Pain Medicine for a contract template.
 - Pretreatment agreement to random urine toxicology screens
 - Use of a stepwise approach to analgesia. See **Pain Medications - Dosage and Indications**, p. 31.
 - Use of non-psychotropic pain medications, when possible, to achieve pain relief
 - When opiates are indicated, use the minimum dosage needed to relieve pain
 - Around-the-clock dosing is more effective than use as needed
 - Ensuring that adequate pain relief is obtained to prevent self-medication: Increasing dosages may be required if the underlying cause of pain (e.g., malignancy) progresses or tolerance develops
 - Referral to a pain specialist for complex management issues or concerns over drug-seeking behavior



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KEY POINTS

- Smoking is the leading cause of preventable death and disease in the United States, accounting for approximately 480,000 deaths each year. It is a chronic, relapsing disorder that often requires repeated interventions and multiple attempts to quit.
- Patient interest in smoking cessation is high (>66% in most surveys).
- Patients infected with HIV are 2-3 times more likely to be smokers than their age-matched counterparts not infected with HIV.
- Smokers infected with HIV face traditional tobacco-related risks, such as cardiac disease, stroke, COPD, and osteoporosis. These conditions are likely to become more prevalent with the aging of the HIV infected population on effective ARV.
- Smoking and HIV infection substantially increase the risks of respiratory tract infection, including acute bronchitis, bacterial pneumonia, PCP, and TB. In a large study of persons infected with HIV in North America and Europe, the mortality rate ratio of smokers versus non-smokers was 1.94.
- Smokers infected with HIV are at higher risk of several tobacco related cancers, and may be at increased risk of poorer immunologic and virologic responses to ARV.
- Asking patients about smoking is an important part of primary care management. Current users should be asked about smoking at every visit.
- Brief (<3 min) tobacco dependence interventions are effective, and every tobacco user should be offered treatment.
- Counseling and medication are effective when used by themselves for treating tobacco dependence. The combination of counseling and medication, however, is more effective than either alone.
- Evidence-based treatment options include behavioral counseling and support, nicotine replacement therapy, and bupropion. Varenicline is a second-line option at the VHA for patients who fail other therapies and do not have suicide or violence risks.

Note: Current information on VHA smoking and tobacco use cessation policy and tools can be found online at VA Tobacco and Health website, <https://www.mentalhealth.va.gov/quit-tobacco/>.



BACKGROUND

- Smoking is a cause of cancers of the bladder, cervix, esophagus, kidney, larynx, lung, oral cavity, pancreas, and stomach; of leukemia; of peripheral atherosclerosis, cerebrovascular disease, and coronary artery disease; of COPD, decreased lung function, and lung infections; of pregnancy complications; and of peptic ulcer disease.
- Patients infected with HIV are 2-3 times more likely to be smokers than their age matched counterparts not infected with HIV.

Note: Some medications mentioned in this chapter may not be available on the VHA National Formulary (<https://www.pbm.va.gov/NationalFormulary.asp>). Consult VA pharmacists for alternatives.

- In the United States, up to 65% of patients in HIV primary care clinics are smokers.
- Smokers infected with HIV have higher rates of certain diseases (compared with smokers not infected with HIV and nonsmokers infected with HIV), such as lung cancer, head and neck cancers, anal and cervical cancers, oral candidiasis, and oral hairy leukoplakia.
- HIV infection increases the risk of respiratory tract infections, and smoking further increases the risks of acute bronchitis, bacterial pneumonia, PCP, and tuberculosis.
- Smoking may decrease the immunologic and virologic response to ARV. In a cohort of HIV-infected women, smokers had lower CD4 cell counts and higher HIV viral loads compared with age-matched female nonsmokers infected with HIV after initiation of ARV.
- Smoking is the leading cause of preventable death and disease in the United States. Tobacco use is a chronic, relapsing disorder that often requires repeated interventions and multiple attempts to quit.
- Most smokers are interested in quitting. Surveys have found that two thirds of smokers infected with HIV want to quit.
- Quitting before age 40 reduces the risk of dying from smoking-related illness by 90%.
- Smoking cessation programs for smokers infected with HIV are effective. For example, among patients who were given a 10-week supply of nicotine patches, self-help booklets, and initial physician counseling plus (by randomization) eight counseling phone calls or no calls, 37% of those in the counseling group were not smoking at a 3-month follow-up, compared with 10% of those who did not receive the counseling phone calls.

There are several high-risk groups with higher rates of tobacco abuse and increased difficulty of achieving successful cessation. These include patients with a serious mental illness (depression, bipolar disorder, anxiety, schizophrenia, and post-traumatic stress disorder), substance abuse, heavy alcohol use, chronic pain, the homeless, and those living with a smoker.

Female Veteran smokers have distinct characteristics compared to their male counterparts. In general, they are lighter smokers, but have a greater degree of behavioral dependence, are less successful at quitting, are more likely to relapse in response to stress, and are more adversely impacted by nicotine withdrawal.



EVALUATION

The 5 A's

These strategies are designed to be brief (<3 minutes of direct clinician time). They need not be delivered by the same clinician; for example, a clinic nurse may ask about tobacco use, whereas a prescribing clinician (e.g., MD, PA, or NP)

may advise, assess, and assist, with referral to another provider for counseling services.

ASK ...

- All patients about tobacco use at every clinic visit:
 - If a patient has never used, you do not need to ask again.
 - If a patient quit years ago, congratulate and check in periodically.
 - Consider making it a part of your office practice to ask about and record tobacco use while patients are having vital signs recorded.



ADVISE ...

- Smokers with clear, strong, and personalized suggestions:
 - **Clear:** “I think it is important that you quit smoking. I can help.”
 - **Strong:** “Quitting smoking is one of the most important things you can do to protect your health.”
 - **Personalized:** Associate smoking with something that is important to the patient, such as exposure of children to tobacco smoke, the expense of cigarettes, or pulmonary and cardiovascular comorbidities. “Remember the time you had that terrible pneumonia?” “Do you realize that you can save almost \$2,000 a year on cigarette expenses if you quit?”



ASSESS ...

- Smokers’ readiness to quit within 30 days: “Are you willing to give quitting a try in the next 30 days?”
- If not ready, consider using motivational interviewing to increase patient’s readiness to quit. See the **5 R’s for Patients Unwilling to Quit**, below*.
- If ready, **assist** and **arrange** (following).



ASSIST ...

- A patient’s preparations for quitting:
 - Setting a quit date. Ideally, the quit date should be within 2 weeks.

- Telling family, friends, and coworkers about quitting, and requesting understanding and support.
- Anticipating challenges to the upcoming quit attempt, particularly during the critical first few weeks. These include nicotine withdrawal symptoms.
- Removing tobacco products from the environment. Before quitting, avoiding smoking in places where a lot of time is spent (e.g., work, home, car). Making the home smoke free.
- Offer nicotine replacement (ideally, combination nicotine replacement, e.g. nicotine patch and nicotine lozenges) or, if appropriate, bupropion, varenicline, or other medication. See below for more details on medication options.
- Provide practical counseling (problem-solving/skills training; see below).
- Offer intensive treatment options (smoking cessation intervention programs and groups).
- Offer readily available counseling and support services: phone support, clinic counselors.



ARRANGE ...

- Enrollment in a VHA-based smoking cessation clinic, if the patient wishes.
- Referral to appropriate counseling services.
- Referral to evidence-based cessation programs such as the VA Quit Line at 1-855-Quit-VET).
- Follow-up contact during the first week after quit date (in person or by phone).
- Follow-up visit 1 month after quit date.
- Subsequent follow-up visits; congratulate upon success in quitting; anticipate further support with relapses (approximately 35–40% patients relapse 1–5 years after quitting).

Adapted from Fiore et al. See **References**.

* For more detailed suggestions on how to conduct motivational interviewing with smokers, see Fiore et al. Chapter 3, Section B. See **References**.

Rx MANAGEMENT

Current tobacco users who are not ready to quit: continue to encourage smoking cessation.

The 5 R's for Patients Unwilling to Quit

- **Relevance:** Explain to patients why cessation is personally relevant (e.g., comorbidities, cost).
- **Risks:** Ask patients to explain their perceived potential risks of smoking; discuss these risks with them (e.g., sexual dysfunction, infertility, fetal harm, cardiovascular and pulmonary disease, malignancies, second-hand smoke). Explain that:
 - 20 minutes after quitting, heart rate and blood pressure drop
 - 12 hours after quitting, carbon monoxide levels drop to normal
 - 2 weeks to 3 months after quitting, circulation and lung function improve
 - 1 year after quitting, risk of coronary heart disease is cut in half
 - 5 years after quitting, stroke risk is the same as for nonsmokers
 - 10 years after quitting, lung cancer risk is cut in half
- **Rewards:** Ask patients to explain what they might gain from cessation (e.g., breath smells better, stained teeth get whiter, bad odor of clothes goes away, food tastes better, sense of smell returns to normal, everyday activities do not result in shortness of breath, skin tone gets better, health improves, worries about secondhand smoke lessen, respiratory symptoms improve, lung function improves, muscle mass and bone density increase).
- **Roadblocks:** Ask patients to identify barriers to quitting (e.g., fear of failure, weight gain, depression) and offer options to address those barriers.
- **Repetition:** Discuss these issues with patients at each visit.

Adapted from Fiore et al. See **References**.

Current tobacco users who are ready to quit:

- Offer smoking cessation treatment at every visit to every patient who smokes.
- For patients with symptoms suggestive of COPD, particularly shortness of breath, consider pulmonary function testing, including spirometry, lung volume, and diffusion studies, and provide medication to support a quit attempt.
- Patients who are informed of abnormal pulmonary function test results may be more likely to quit.
- If applicable, discuss challenges patients have encountered during previous attempts to quit and tailor current recommendations to what patients can accomplish.
- Research strongly supports treatment in the form of behavioral counseling (even brief sessions [<3 minutes]) and first-line smoking cessation medications. Specifically, U.S. Public Health Service's (USPHS) 2008 update of the Clinical Practice Guideline on Treating Tobacco Use and

Dependence (see **References**, Fiore et al.) finds strong evidence in favor of:

- Using medications to assist in smoking cessation
- Combining medication with behavioral counseling
- Providing multiple counseling sessions as opposed to single counseling sessions
- Pharmacologic interventions below are effective medications recommended by the USPHS. First line therapies include nicotine replacement (preferably and more effective in combination) and Bupropion (also more effective in combination with nicotine replacement). Varenicline can be an option and a second line option. (Do not combine with nicotine replacement).
- Two components of counseling have been found to be particularly effective: working with patients to develop **problem-solving skills** and strategies, and delivering **social support** as part of counseling.

Examples of Problem-Solving Skills

Type of Skill	Examples
Identifying situations that endanger smoking cessation	<ul style="list-style-type: none">• Negative stressors• Being around smokers• Alcohol• Smoking cues• Availability of cigarettes
Identifying coping skills	<ul style="list-style-type: none">• Learning to anticipate and avoid tempting situations• Cognitive strategies for• improving mood, decreasing stress• Changing routines that expose the patient to smoking cues
Identifying feelings that can threaten cessation	<ul style="list-style-type: none">• A single puff increases the risk of relapse• Withdrawal symptoms peak 1-2 weeks after quitting but may persist for months• Withdrawal symptoms can include negative mood, urges to smoke, difficulty concentrating

Adapted from Fiore et al. See **References**.

Examples of Social Support

Type of Support	Examples
Encouragement to quit	<ul style="list-style-type: none"> • Effective treatments are available • Half of people who have ever smoked have been able to quit • Communicate belief in patient's ability to quit
Communicate caring and concern	<ul style="list-style-type: none"> • Ask how patient feels about quitting • Express willingness to help as often as needed • Ask about patient's fears and ambivalence about quitting
Encourage patient to talk about the quitting process	<ul style="list-style-type: none"> • Ask the patient why they want to quit • Ask about the patient's concerns about quitting • Ask what successes and difficulties in quitting has patient had in past

Adapted from Fiore et al. See **References**.

- Continue to encourage cessation even if the patient relapses. Relapse does **not** mean that the patient will not quit successfully on a future attempt.
- Control of depression increases the odds of successful smoking cessation.
- Counsel patients on potential nicotine withdrawal symptoms. Note that 25% of smokers who quit do **not** have these symptoms. Nicotine withdrawal symptoms include:
 - Depressed mood
 - Insomnia
 - Irritability
 - Anxiety
 - Difficulty concentrating
 - Restlessness
 - Decreased heart rate
 - Increased appetite and weight gain (10% of patients gain >13 kg after smoking cessation)

Pharmacologic Interventions

Key Points

- Nicotine replacement therapies (NRTs) such as nicotine patch, gum, and lozenges, do not interact with ARVs and have low toxicity at recommended dosages, even in patients with cardiovascular disease.
- Combination NRT regimens have achieved better 6-month abstinence rates in several trials of than the use of a single product. The nicotine patch is used to deliver a consistent level of nicotine, and the gum or lozenge is used to minimize symptom flares as needed during the day.
- Bupropion with the nicotine patch or bupropion with PRN nicotine lozenges also achieved better 6-month abstinence rates in several trials than use of the patch alone.
- Combining varenicline with the nicotine patch did not improve abstinence rates compared to varenicline alone and from a pharmacologic standpoint, it doesn't make sense to use varenicline with nicotine.

Varenicline is a safe medication in patients without mental illnesses and in patients with stable mental illnesses. In rare instances, varenicline has been associated with violent thoughts, intent, or actions toward oneself or others, mostly in uncontrolled mental illnesses. If patient has mental illnesses, consult their mental health provider before prescribing. It is a second-line medication for patients who have failed any trial of NRT, bupropion, or combination therapy. The role of electronic nicotine delivery systems (ENDS) in smoking cessation is controversial and not recommended. There is no clear evidence that it helps with cessation and is no longer marketed as such. In addition, FDA has announced extending tobacco regulation to include ENDS. Safety is not established as well.

VHA Formulary Choices for Pharmacotherapy of Smoking Cessation: Bupropion, Nicotine Replacement Therapy (NRT), and Varenicline

	Bupropion	Nicotine Transdermal Patch	Nicotine Polacrilex Gum	Nicotine Polacrilex Lozenge	Varenicline
Formulations	Bupropion SR 150 mg. (Other formulations can be used)	(Nicoderm/Habitrol) 21 mg, 14 mg, 7 mg (Nicotrol) 15 mg, 10 mg, 5 mg	2 mg, 4 mg	2 mg, 4 mg	0.5 mg, 1 mg
Start instructions	1-2 weeks before target quit date	On target quit date	On target quit date		1 - 2 weeks before target quit date
Recommended regimen	Bupropion SR 150 mg daily for 3 days, then 150 mg twice a day; Reduce dosage in cirrhosis or trial other options: 150 mg every other day Strongly recommend to use in combination with Nicotine lozenges nicotine gum or nicotine patch.	High dependence# 21 mg for 4-6 weeks, then 14 mg for 2-3 weeks, then 7 mg for 2-3 weeks Low dependence 14 mg for 6-8 weeks, then 7 mg for 2 weeks Medications can be used for longer. On average about 3-4 months for tapering but can extend to up to 6 months or a bit longer if needed.	Note this is for monotherapy. Strongly encourage use in combination with patch or bupropion. See combination therapy section for details. High dependence# 4 mg every 1-2 hour for 6 weeks, then every 2-4 hour for 3-4 weeks, then every 4-6 hour for 2-3 weeks	Note this is for monotherapy. Strongly encourage use in combination with patch or bupropion. See combination therapy section for details. *High dependence# 4 mg Low dependence 2 mg Suck 1 lozenge every 1-2 hour for 6 weeks, then 1 lozenge every 2-4 hour for 3 weeks, then 1 lozenge every	Initial: 0.5 mg daily on days 1-3, then 0.5 mg twice a day on days 4-7, then 1 mg twice a day for total duration of 12 weeks Reduce dosage for CrCl <30: maximum dosage 0.5 mg twice a day; end-stage renal disease or hemodialysis: 0.5 mg daily

Bupropion	Nicotine Transdermal Patch	Nicotine Polacrilex Gum	Nicotine Polacrilex Lozenge
-	-	<p>Low dependence 2 mg every 1-2 hour for 6 weeks, then every 2-4 hour for 3 weeks, then every 4-6 hour for 3 weeks Maximum: 24 pieces/24 hours</p> <p>Alternative strategy can focus on the # of nicotine gum vs. duration. Use minimum of 9 pieces up to the maximum of 24 per day and then reduce by 1-2 each week.</p> <p>Medications can be used for longer. On average about 3-4 months for tapering but can extend to up to 6 months or a bit longer if needed.</p>	<p>-</p> <p>4-8 hour for 3 weeks Maximum: 20 lozenges/24 hours or 5 lozenges/6 hours</p> <p>Alternative strategy can focus on the # of nicotine lozenge vs. duration. Use minimum of 9 pieces up to the maximum of 20 per day and then reduce by 1-2 each week.</p> <p>Medications can be used for longer. On average about 3-4 months for tapering but can extend to up to 6 months or a bit longer if needed.</p>

	Bupropion	Nicotine Transfer mal Patch	Nicotine Polacrilex Gum	Nicotine Polacrilex Lozenge	Varenicline
Administration comments	<ul style="list-style-type: none"> • Start 1-2 weeks before quitting smoking (to achieve steady-state levels) • Continue treatment for 8-12 weeks (if not quit by week 8, consider discontinuation and other options) • Some may need longer than 12 weeks • Bupropion may cause insomnia, so advise patients to take evening dose in afternoon • If a patient has mental illness, consult with their provider before initiating 	<ul style="list-style-type: none"> • Usually worn 24 hours • May remove overnight if vivid dreams or trouble sleeping occurs • Apply on upper arm, chest or back • Rotate sites (avoid same area for a week) • Can shower or swim with it (medical tape can be used if needed) • Do not cut the patch 	<ul style="list-style-type: none"> • Chew slowly (about 10 chews) until peppery taste is released, then “park” between teeth and gums until flavor dissipates; repeat process on and off for 30 minutes per piece • Has been studied in combination with patch 	<ul style="list-style-type: none"> • Allow lozenge to dissolve slowly over 20-30 minutes (less if using mini-lozenges), shifting in mouth occasionally • Do not chew or swallow (increased risk of GI side effects) • Avoid acidic beverages within 15 minutes of use (e.g., citrus juices and soft drinks); these decrease absorption 	<ul style="list-style-type: none"> • Screen for suicide and violence risk before starting (safe for most patients, avoid in patients with active mental illness) • Start 1 week before target quit date • Take drug after eating and with 8 oz of water • Instruct patient or caregiver to report depression, suicidal ideation, unusual changes in behavior, or worsening of preexisting psychiatric illness • An additional 12 weeks of treatment in patients who have successfully stopped smoking may increase likelihood of long-term abstinence

	Bupropion	Nicotine Transdermal Patch	Nicotine Polacrilex Gum	Nicotine Polacrilex Lozenge	Varenicline
ARV Interactions	Metabolized by the cytochrome P450 system; efavirenz and tipranavir may ↓ bupropion levels 40-50%; when using with these ARVs, monitor for depression and titrate to clinical effect; ritonavir may ↑ bupropion levels		None		Does not interact with the cytochrome P450 system; no ARV interactions identified to date
Time to peak blood concentrations	3 hours (half life = 21 hours)	4-10 hours	15-30 minutes	No data, similar to nicotine gum, slightly quicker	3-4 hours
Absorption	20%	75-90%	30%	30%	High; virtually complete absorption
Advantages (+) Disadvantages (-)	(+) Good adherence; ease of use; can be combined with nicotine replacement; such as nicotine lozenge,	(+) Best adherence; easy to use; consistent rate of exposure; unobtrusive	(+) Helps prevent sudden urges; can titrate to adjust for cravings; and ease to taper; behavioral	(+) Easy to use; discreet; higher immediate levels; can titrate to adjust for cravings; reduces self-reported	(+) Good adherence; ease of use; consistent rate of exposure; higher rate of abstinence compared with

Bupropion		Nicotine Transdermal Patch	Nicotine Polacrilex Gum	Nicotine Polacrilex Lozenge	Varenicline
-	<p>nicotine gum or nicotine patch; consistent rate of exposure; helps with withdrawal symptoms</p> <p>(-) Some minor drug interactions resulting from metabolism by CYP 2B6; CNS side effects; increased risk of seizures; avoid in hepatic insufficiency</p> <p>*consult MH provider if patient has active mental illness or have any other MH diagnosis.</p> <p>*Avoid use in liver cirrhosis patients</p> <p>*Do not use in patients with eating disorders (e.g. anorexia, bulimia)</p> <p>*Avoid use in patients with active substance use disorder (SUD)</p>	<p>-</p> <p>(-) Less effective than short acting NRT for cravings; hence emphasis on utilizing in combination; difficult to control titration; absorption increased at elevated temperatures</p>	<p>substitute for cigarettes; slow release of nicotine reduces addiction potential; provide a behavioral substitution</p> <p>(-) Difficult for those with poor dentition or dentures; must learn proper chewing technique; should abstain from smoking while using NRT; must abstain from drinking/eating during gum use; swallowing nicotine causes GI side effects (hiccups, diarrhea or constipation, flatulence, belching)</p>	<p>withdrawal symptoms; provides a behavioral substitution; delivers slightly more nicotine than the nicotine gum</p> <p>(-) Must abstain from drinking/eating during lozenge use; should abstain from smoking while using NRT; swallowing nicotine causes GI side effects (hiccups, diarrhea or constipation, flatulence, belching)</p>	<p>bupropion and placebo</p> <p>(-) possible potential for rare serious neuropsychiatric side effects, particularly in patients with underlying psychiatric disease or violence risk; dosage adjust for renal insufficiency (CrCl <30); high incidence of nausea; not studied in patients with underlying mental illness</p>

	Bupropion	Nicotine Transdermal Patch	Nicotine Polacrilex Gum	Nicotine Polacrilex Lozenge	Varenicline
Adverse effects	<ul style="list-style-type: none"> • Anxiety • Disturbed concentration • Dizziness • Insomnia • Constipation • Dry mouth • Nausea • Seizures (risk:1:1,000) 	<ul style="list-style-type: none"> • Sleep disturbances/vivid dreams (note doesn't cause nightmares but can aggravate existing ones) • Local skin irritation (common but alternating sites prevent this) • Bone pain • Headache • Nausea 	<ul style="list-style-type: none"> • Local mouth irritation • Jaw pain • Hiccups • Dyspepsia • Rhinitis • Nausea 	<ul style="list-style-type: none"> • Local mouth irritation/tingling • Heartburn, indigestion, nausea (if chewed) • Headache • Nausea, diarrhea • Flatulence 	<ul style="list-style-type: none"> • Dream disorders • Headache • Insomnia • Agitation/Aggression • Depressed mood • Suicidal thoughts • Constipation • Flatulence • Nausea, vomiting <p>Consider dosage reduction for patients sensitive to adverse effects (e.g, nausea, headache, insomnia)</p>
VHA National Formulary restrictions	None	None	None	None	<ul style="list-style-type: none"> • This is a second line medication after failure of nicotine patch, nicotine gum, nicotine lozenge, bupropion or combination therapy. • If appropriate 28 days with no refills can be given

	Bupropion	Nicotine Transdermal Patch	Nicotine Polacrifex Gum	Nicotine Polacrifex Lozenge	Varenicline
-	-	-	-	-	<ul style="list-style-type: none"> • Within 28 days of initiation, 1 mood assessment is needed (generic assessment; no standard questions). If stable 28 days and 1 refill may be provided. • Should be tobacco free within 12 weeks, and another 12 weeks can be provided thereafter <p>No restrictions on how many times a year the medication can be tried</p> <p>Relative contraindications:</p> <ul style="list-style-type: none"> • Serious neuropsychiatric disorders (including suicidal and homicidal ideation)
Contraindications and relative contraindications/Precautions	<p>Contraindications:</p> <ul style="list-style-type: none"> • History of seizures • Predisposition to seizures (e.g., severe head trauma, CNS tumor, cirrhosis) • Abrupt withdrawal 	<p>Relative contraindications:</p> <ul style="list-style-type: none"> • Hypersensitivity (patch could be due to the adhesive, so if hives, then stop using) • Pregnancy category D • Use within 14 days post MI, or in patients with serious or worsening angina 			<p>Relative contraindications:</p> <ul style="list-style-type: none"> • Serious neuropsychiatric disorders (including suicidal and homicidal ideation)

	Nicotine Transdermal Patch	Nicotine Polacrilex Gum	Nicotine Polacrilex Lozenge	Varenicline
<p>Bupropion</p> <p>from heavy, daily alcohol or other sedative</p> <ul style="list-style-type: none"> MAO inhibitor within 14 days Bulimia, anorexia nervosa <p>Relative contraindications:</p> <ul style="list-style-type: none"> Hypersensitivity Pregnancy category B 	-	-	-	<ul style="list-style-type: none"> History of suicidal, homicidal, or assaultive behavior in the past 12 weeks Untreated or unstable mental disorder such as psychotic disorder, bipolar disorder, major depressive disorder, and PTSD Severe renal impairment <p>Pregnancy category C</p> <p>Precautions:</p> <ul style="list-style-type: none"> Case reports of seizures, avoid if possible Reports of lowering tolerance to alcohol

	Bupropion	Nicotine Transdermal Patch	Nicotine Polacrilex Gum	Nicotine Polacrilex Lozenge	Varenicline
Comments	<ul style="list-style-type: none"> • Use with caution in patients with liver/kidney failure • Avoid in patients on MAO inhibitors 	<ul style="list-style-type: none"> • In combination with behavioral program, patch doubles the quit rate • Should try to abstain from smoking while using NRT but if having slips, continue using as prescribed (Let slips slide, but if relapse, then hold/stop medication and re-evaluate). 	<ul style="list-style-type: none"> • In combination with an intensive behavioral program, nicotine lozenges can increase the quit rate • Should try to abstain from smoking while using NRT but if having slips, continue using as prescribed (Let slips slide, but if relapse, then hold/stop medication and re-evaluate). 	<ul style="list-style-type: none"> • Ask patients about any psychiatric history before prescribing varenicline • Monitor for signs/symptoms of psychiatric illness during use • Monitor serum creatinine levels; as renal function decreases (as seen in elderly patients), dosage reductions may be necessary 	

High dependence: in general, >20 cigarettes per day or use of first cigarette within 30 minutes of awakening.

Note: Two additional prescription products, a nicotine inhaler and nicotine nasal spray, are FDA approved for NRT; however, these products are not available on the VHA National Formulary. For more information on these products, visit the American Lung Association Smoking Cessation Support website, <http://www.lungusa.org>. VA is not responsible for the content of the linked site.

Preferred Combinations

Therapy	Dosage and Duration	Comments
Nicotine patch + lozenge or gum	<ul style="list-style-type: none"> • Dose Nicotine patches the same as monotherapy dosing. • Lozenges and gum are used as needed, but initially should be used more consistently. • See infographic below for complete dosing instructions. 	<ul style="list-style-type: none"> • Lozenges and gum allow for bridging increase urges/cravings when stepping down on lower dose patches. • Lozenges and gum also assist with increase cravings/urges but allow for behavioral substitutions. • Combination NRT (Patch ± lozenge or gum) is more effective than monotherapy and as effective as varenicline. <p>Patch + gum had 36.5% 6-month abstinence rate in trials vs. 23.4% with patch alone (meta-analysis).</p>
Bupropion ± lozenge, gum or nicotine patches	<ul style="list-style-type: none"> • Dose Bupropion the same as monotherapy dosing. <p>When using lozenges or gum:</p> <ul style="list-style-type: none"> • Lozenges and gum can be dosed similarly to monotherapy dosing, but patients likely will use less. • Taper lozenges and gum over 3-4 months (average but can be longer). • Lozenges and gum also assist with increase cravings/urges but allow for behavioral substitutions. <p>When using Nicotine Patches:</p> <ul style="list-style-type: none"> • Dose nicotine patches same as monotherapy. 	<ul style="list-style-type: none"> • Lozenges and gum also assist with increase cravings/urges but allow for behavioral substitutions. • Combination Bupropion + NRT is more effective than monotherapy and as effective as varenicline: Patch + bupropion had 28.9%, and lozenge + bupropion had 29.9% 6-month abstinence rates (Meta-Analysis). • Bupropion use with short acting NRT (lozenges or gum) may be preferred given that lozenges offer a behavioral substitution strategy that the patches do not.

<https://www.publichealth.va.gov/docs/smoking/combo1.pdf>

Preventing or Addressing Relapse with Patients Who Have Quit

- Congratulate patients at each visit and discuss the benefits and challenges of quitting.
- Use open-end questions relevant to the topics below to discover whether the patient wishes to discuss issues related to quitting:
 - The benefits, including potential health benefits, the patient may derive from cessation
 - Any success the patient has had in quitting (e.g., duration of abstinence, reduction in withdrawal)
 - The problems encountered or anticipated threats to maintaining abstinence (e.g., depression, anxiety, chronic pain, weight gain, alcohol, other tobacco users in the household, significant stressors)
 - If the patient is still taking medication, assess effectiveness, side effects, and other medication issues
- Interventions to address barriers to maintaining cessation:
 - Lack of support: Refer patients to a group, schedule follow-up phone calls, help identify potential sources of support (individuals, community or religious organizations).
 - Prolonged withdrawal symptoms: Prolong pharmacologic interventions or consider combination therapy.
 - Depressed mood: Consider using antidepressants and initiating psychotherapy.
 - Weight gain: Reassure patients that weight gain is common and self-limited, encourage patients to increase exercise, counsel on a healthy diet (avoid strict dieting), preferentially use pharmacologic interventions that cause less weight gain (e.g., bupropion, nicotine gum).
 - Flagging motivation: Reassure patients that flagging motivation is common, check to see if patients might be using tobacco periodically, and counsel that taking even a single puff will increase urges and make quitting more difficult.
 - Smoking lapses: Suggest continued use of medications, which can reduce the likelihood that a lapse will lead to a full relapse. Encourage another quit attempt or a recommitment to total abstinence. Reassure that quitting may take multiple attempts, and use the lapse as a learning experience. Provide or refer for intensive counseling.
 - In patients with mental health problems, extending maintenance pharmacotherapy to one year improves sustained abstinence rates.



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Mental Health

Depression

KEY POINTS

- Depression can be a life-threatening disorder.
- Depression among people with HIV is common and is associated with increased high-risk behavior; decreased physical activity, nonadherence to antiretroviral therapy (ARV), and progression of immunodeficiency.
- Depression can be diagnosed and treatment can be initiated in the primary care setting.
- Tools such as the Patient Health Questionnaire (PHQ) can be used for screening and for ongoing monitoring of patients identified as depressed.
- Potentially treatable causes of secondary depressive symptoms in HIV-infected persons should be investigated and treated.
- Antidepressant medication and psychotherapy both have a role in treatment of HIV-infected persons with depression.

Linking Primary Care and Mental Health Care Services in the Treatment of Depression

VA medical centers and community-based outpatient clinics integrate mental health services into primary care settings. Clinic structures and services vary from one facility to another. Primary care providers should be familiar with local practices on referring patients for mental health consultation.



WHEN TO REFER

Indications for referring depressed patients to a mental health care provider:

- Disabling symptoms - Presence of functional impairment at work/school, in social relationships, or self-care
- Suicidal thought with plan or intent
- Severe hopelessness or negativism
- Persistent agitation
- Psychotic symptoms
- Pronounced affective instability
- Suspected bipolar disorder
- Three or more ineffective therapeutic trials of antidepressant medication
- Complicated psychopharmacologic regimens requiring medications which the provider is not experienced in prescribing
- Need for tricyclic antidepressants (TCAs)

Note: Some medications mentioned in this chapter may not be available on the VHA National Formulary (<https://www.pbm.va.gov/NationalFormulary.asp>). Consult VA pharmacists for alternatives.



BACKGROUND

- Lifetime prevalence of depression among HIV-infected persons in the United States is 20-40%, up to 2-fold higher than it is among HIV-uninfected persons. Among Veterans, this percentage may even be higher.
- The risk of suicide mortality in HIV-infected persons is 3-5 times higher than in HIV-uninfected counterparts, despite the availability of ARV therapy.
- Depression increases the risk of acquiring HIV infection and the likelihood of high-risk sexual behavior among persons already infected with HIV.
- Depression is associated with nonadherence to ARV therapy, progression of HIV disease, and decline in CD4 cell count.
- Treatment of depression improves adherence to ARV therapy.

Veterans with HIV

In fiscal year 2015, among Veterans served by the Veterans Health Administration (VHA), the documented prevalence of any depression (including depression not otherwise specified) was 19.8% while the documented prevalence of major depressive disorder (MDD) only was 6.5%. Of Veterans admitted to the hospital in 2011 with serious illnesses including HIV/AIDS, 11.4% were diagnosed with depression.



EVALUATION

Note: The VA has published guidelines for evaluation and treatment of depression. See **References**.



SCREENING

Recommended Screening for Depression in Primary Care Settings

The VA recommends using the PHQ-2 and PHQ-9 instruments to screen for depression in the primary care setting, a use for which they are validated. The VA also recommends that the result of screens be entered in the chart on the day the screens are administered. Telephone screening is acceptable, provided that positive screening results are addressed by appropriate risk assessments and interventions.

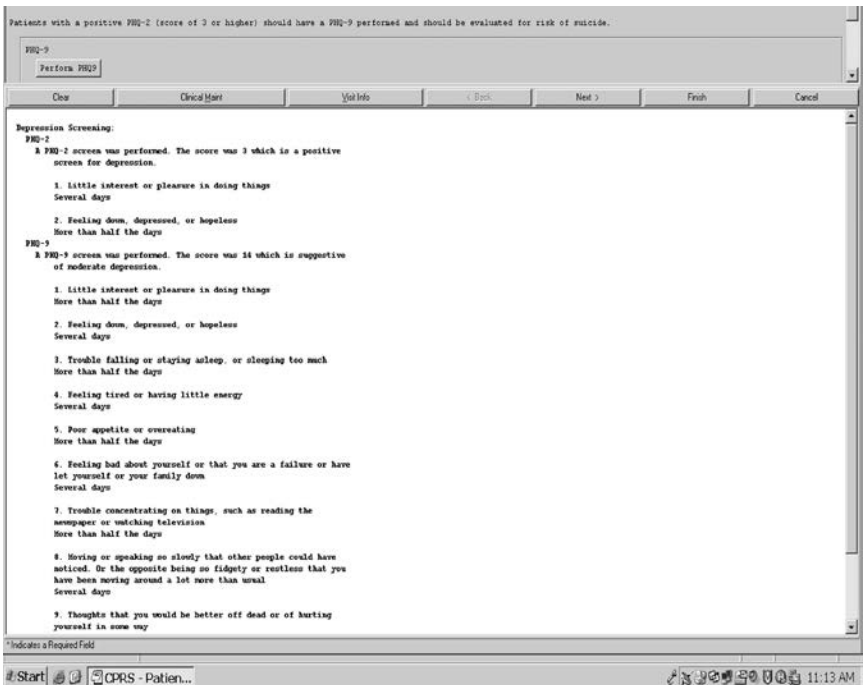
PHQ-2 and PHQ-9

The PHQ-2 is a two-question screen. The maximum score is 6, and a positive score is 3. If the PHQ-2 result is negative, further screening is unnecessary. If the PHQ-2 result is positive, further screening becomes necessary. In most VAs, a positive PHQ-2 automatically triggers the VHA Pocket Card Suicide Risk Questions, a three-item screening (see below for the Pocket Card items). The patient must be screened on the same day. A PHQ-9 is also used, with responses to all questions and the summary score to be recorded in the patient's chart. Alternatively, the patient can be screened with the PHQ-9 alone, with responses to all questions and the summary score to be recorded in the patient's chart.

Patients who screen positive for depression should be evaluated for risk factors that indicate a need for urgent intervention. Foremost in this process is an explicit assessment for the presence of suicidal ideation. After an evaluation of screening results and a discussion with the patient, the provider can decide whether the patient may benefit from urgent intervention or further specialized mental health evaluations.

Note: The CPRS Clinical Reminder supporting the standard PHQ-2 and PHQ-9 tools will display the questions comprising these instruments when the “Perform PHQ-2” and “Perform PHQ-9” buttons are selected, and it allows for documentation of depression screen results. Figure 1 is an example:

Figure 1. CPRS Clinical Reminder, Depression Screening



Acceptable screening is summarized as follows:

Screening Tool Used	PHQ-2 Result	PHQ-9 Result
PHQ-2	Negative	Not required
PHQ-2	Positive	Required on same day
PHQ-9	Not required	NA

The Patient Health Questionnaire – 2 (PHQ-2)				
Patient Name: _____			Date of Visit: _____	
Over the past two weeks, how often have you been bothered by any of the following problems?	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
Total point score: _____				

Scoring the PHQ-2		
PHQ-2 Score	Positive Predictive Value Probability of Major Depressive Disorder (%)	Positive Predictive Value Probability of Any Depressive Disorder (%)
1	15.4	36.9
2	21.1	48.3
3	38.4	75.0
4	45.5	81.2
5	56.4	84.6
6	78.6	92.9

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The Patient Health Questionnaire – 9 (PHQ-9)				
Over the last 2 weeks, how often have you been bothered by any of the following problems?	Not at all	Several days	More than half the days	Nearly every day

The Patient Health Questionnaire – 9 (PHQ-9)

1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself – or that you are a failure or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed, or the opposite – being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3
9. Thoughts that you would be better off dead, or of hurting yourself in some way	0	1	2	3
Add columns:				
	0	+ ____	+ ____	+ ____
	= Total Score: _____			
If you checked off <i>any</i> problems, how <i>difficult</i> have these problems made it for you to do your work, take care of things at home, or get along with other people?				
Not difficult at all	Somewhat difficult		Very difficult	Extremely difficult
<input type="checkbox"/>	<input type="checkbox"/>		<input type="checkbox"/>	<input type="checkbox"/>

Scoring the PHQ-9

1-4	Minimal depression
5-9	Mild depression
10-14	Moderate depression
15-19	Moderately severe depression
20-27	Severe depression

Clinicians should be particularly alert to patients' responses to question 9, "Thoughts that you would be better off dead, or of hurting yourself in some way." **Any** affirmative response to question 9, or a PHQ-9 score of >9, requires that a suicide risk assessment be completed within 24 hours. See below.

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The PHQ-9 is validated for use only with English-speaking persons of European origin; some experts feel it is less sensitive for depression in many patients with Asian or Latino backgrounds. As with all symptom questionnaires, assessment results should be interpreted and guided by clinical experience.

Suicide Risk Screen Pocket Card

Are you feeling hopeless about the present or future?

Have you had recent thoughts about taking your life?

Do you have a plan to take your life?

Have you ever had a suicide attempt?

Clinical Interpretation of Preliminary Suicide Risk Screen

If positive: A comprehensive suicide risk assessment should be completed immediately and documented in CPRS.

If negative: No further action is needed at this time.

Assessment of Suicide Risk

Veteran suicide is a serious public health issue, and HIV infection also puts patients at risk of suicidality. Primary care providers are on the front line in identifying Veterans with risk factors for suicide and ensuring they receive appropriate interventions. An affirmative response to questions about suicidality on screening instruments, such as the PHQ-9, should prompt further investigation. When the PHQ-9 is used, a score of >9 or any affirmative response to question 9 suggests that a suicide risk screening (e.g., the VHA Pocket Card Suicide Risk Questions screening or the local facility's Comprehensive Suicide Risk Assessment) should be performed within 24 hours; ideally, this risk assessment should immediately follow a positive screening result for depression.

Such assessments may be performed by telephone, provided that the assessment is made by an acceptable provider, and that the results are appropriately documented. An acceptable provider is an MD, NP, DO, PsyD or PhD Psychologist, LCSW, APN, PA (or a trainee with appropriate co-signature), or other allied health care professional who, by virtue of educational background *and* approved credentialing, privileging, or scope of practice, has been determined by the facility to be capable of diagnosing and treating mental illness.

All VA medical centers have a designated suicide prevention coordinator, whose role includes providing general consultation to clinicians concerning risk assessment, providing resources for suicidal individuals, and ensuring that high risk patients receive education and support about approaches to reduce risks.

The CPRS contains a detailed suicide risk assessment template; however, at this time, there is no unified national template for comprehensive screening, thus providers should utilize their local version. To assess patients for suicide risk:

- **Look** for warning signs
- **Assess** for risk and protective factors
- **Ask** the questions

1. Look for warning signs

- Threatening to hurt or kill self
- Looking for ways to kill self; seeking access to pills, weapons, or other means
- Talking or writing about death, dying, or suicide

Any of the above warning signs requires immediate attention and referral. Consider hospitalization for safety until complete assessment may be made.

Additional warning signs include:

- Hopelessness
- Rage, anger, seeking revenge
- Acting reckless or engaging in risky activities, seemingly without thinking
- Feeling trapped – like there's no way out
- Increasing alcohol or drug abuse
- Withdrawing from friends, family, or society
- Anxiety, agitation, unable to sleep or sleeping all the time
- Dramatic changes in mood
- No reason for living, no sense of purpose in life

2. Assess for risk and protective factors

Factors that may increase risk for suicide

- Current ideation, intent, plan, access to means (e.g., weapons or drugs that may be lethal)
- Previous suicide attempt or attempts

- Alcohol/substance abuse
- Previous history of psychiatric diagnosis
- Impulsivity and poor self-control
- Hopelessness – presence, duration, severity
- Recent losses – physical, financial, personal
- Recent discharge from an inpatient unit
- Family history of suicide
- History of abuse (physical, sexual, or emotional)
- Comorbid health problems, especially a newly diagnosed problem or worsening symptoms
- Age, gender, race (elderly or young adult, unmarried, white, male, living alone)
- Same-sex sexual orientation
- Transgender identity

Factors that may decrease risk for suicide

- Positive social support
- Spirituality
- Sense of responsibility to family
- Children in the home, pregnancy
- Life satisfaction
- Reality-testing ability
- Positive coping skills
- Positive problem-solving skills
- Positive therapeutic relationship

3. Ask the questions

Note: Asking about suicide does not induce patients to contemplate killing themselves.

- Are you feeling hopeless about the present/future? If yes, ask ...
- Have you had thoughts about taking your life? If yes, ask ...
- When did you have these thoughts and do you have a plan to take your life?
- Have you ever had a suicide attempt?

Response to Suicide Risk

- **Assure the patient's immediate safety and determine the most appropriate treatment setting.**
- Refer for mental health treatment in a clinically indicated timeframe or assure that follow-up appointment is made.
- Consult with the facility suicide prevention coordinator.

- Inform and involve someone close to the patient with patient's consent.
- Limit access to means of suicide, including firearms. If the Veteran is unwilling to remove firearms (e.g., having a trusted friend hold them temporarily), consider offering a gun lock during the session or discussing other ways of securing all weapons (e.g., lock firearm and store ammunition separately).
- Increase contact and make a commitment to help the patient through the crisis.
- Provide number of ER or urgent care center to the patient and significant others.
- Veteran's Crisis Line (formerly the National Suicide Prevention Lifeline): 800-273-TALK (800-273-8255, press 1). Offer the Veteran and their family/caregiver information about the Veteran's Crisis line, which is available 24 hours a day, 7 days a week, 365 days a year.

Depressive Symptoms Associated with Illnesses Other than Major Depression

Given the overlap between symptoms of depression and symptoms of other illnesses and medication side effects common among persons infected with HIV, all potentially treatable or reversible causes of depression should be considered when persons infected with HIV present with depressive symptoms. The reciprocal relationship between symptoms and depression may be a recurring cycle. Early detection and treatment of depressive symptoms is an important part of proper management of both HIV-related symptoms and medication adherence.

Screening	<ul style="list-style-type: none"> • PHQ-2 • PHQ-9
History	<ul style="list-style-type: none"> • Relationship between onset of depression symptoms and major life stressors • Concurrent chronic disease • Medication history, including recent changes • Use of alcohol or other psychoactive drugs, whether legal or illegal • Past history of depression • Suicidal thoughts • Family history of mental illness
Physical examination	<ul style="list-style-type: none"> • Mini mental status • Neurologic screening • Signs of hypogonadism • Signs of hypothyroidism

Laboratory studies	<ul style="list-style-type: none"> • Low serum zinc concentration • Serum electrolytes • BUN/creatinine • Calcium (for hypercalcemia) • Complete Blood Count (CBC) (for anemia) • Thyroid Stimulating Hormone (TSH) • Serum testosterone • Hepatitis serologies • Rapid Plasma Regain (RPR)
Differential diagnosis	<ul style="list-style-type: none"> • Mood disorders • Major depression • Bipolar affective disorder • Dysthymia (minor depression) • Demoralization • Drug use • Alcohol use/abuse • Anemia • HIV-associated dementia, other dementia • Hypercalcemia • Renal failure • Hepatitis • Hypothyroidism • Hypogonadism • Drug effects or side effects (e.g., EFV*, anabolic steroids, corticosteroids, sedative-hypnotics, beta-blockers, interferon-containing hepatitis C therapy, alcohol, methamphetamine withdrawal) • CNS infections • CNS neoplasms

* EFV is associated with CNS side effects, anxiety, and disturbed sleep (these usually resolve with time), but it has not been shown to convey a higher risk of depressive disorders.

Rx MANAGEMENT

Patients with depressive symptoms who do not require referral to a mental health provider may be managed safely in the primary care setting. There is evidence that treatment with selective serotonin reuptake inhibitors (SSRIs), serotonin–norepinephrine reuptake inhibitors (SNRIs), or tricyclic antidepressants (TCAs) is superior to placebo in relieving symptoms of depression in HIV-infected patients. However, a surprisingly high proportion of placebo recipients in clinical studies also experience symptom relief.

Psychotherapy of many kinds, including cognitive behavioral therapy, acceptance and commitment therapy, social support counseling, and individual psychody-

dynamic therapy, is also effective in treating depression in HIV-infected patients. Comparison of methods is complicated by differences in definitions of depression used in various studies and by the heterogeneity of various scoring instruments.

Interestingly, a study of the effect of treatment of depression on adherence to ARV therapy found that participants treated with psychotherapy or psychotherapy plus medication were more adherent to ARV therapy than those treated with medication alone, or with placebo.

Exercise, even in moderate amounts, may improve or help prevent depressive symptoms. Smoking cessation has also been found to reduce depressive symptoms.

SSRIs, rather than TCAs, are recommended for starting pharmacotherapy for depression, because of the superior safety profile of SSRIs. A patient requiring pharmacologic therapy with an agent other than an SSRI probably should be managed in collaboration with a psychiatrist. Of the SSRIs, citalopram and escitalopram have minimal interactions with ARVs and therefore are frequently chosen for patients on concomitant ARV therapy.

Response to Pharmacotherapy

- Patients typically start responding to SSRIs in 2-4 weeks.
- Patients who show no improvement on maximal-dose therapy after 8 weeks should be switched to another medication or be referred to a psychiatrist.
- Suicidality may remain or emerge during the first several weeks of pharmacologic therapy, even as depression seems to decrease; close follow-up is recommended, with screening for suicidality as needed.

SSRI Discontinuation Syndrome

SSRIs and SNRIs should be tapered slowly rather than discontinued abruptly. Side effects associated with abrupt discontinuation include dizziness, irritability, anxiety, chills, myalgias, and nausea. Symptoms typically occur one day after discontinuing and can last up to two weeks. They remit when the drug is restarted. The discontinuation syndrome is more likely with venlafaxine and shorter-acting SSRIs, such as paroxetine, than with longer-acting agents, such as fluoxetine.

Commonly Used Antidepressant Medications

SSRIs

- **Pros:** Favored by some experts because of low potential for fatal overdose
- **Cons:** Risk of **discontinuation symptoms** with certain agents if discontinued abruptly
- Increased risk of suicidality among children and young adults with depression during first month of taking SSRIs
- **Most common side effects:** sexual dysfunction, nausea, sweating, sleep disturbance
- Contraindicated for use with monoamine oxidase inhibitors (MAOIs) or triptans because of risk of serotonin syndrome
- Interactions with ARVs incompletely studied

Generic Drug Name	Usual Starting Dosage/Dosage Titration	Comments/Drug Interactions
Citalopram	Start at 20 mg QD; may increase daily dosage after 7 days, if no adverse effects; maximum dosage: 40 mg QD.	Metabolized by CYP 3A4; however, no significant change in citalopram levels when coadministered with RTV, and no dosage adjustment required.
Escitalopram	Start at 5-10 mg QD; may increase daily dosage after 7 days, but no evidence of increased efficacy; maximum dosage: 20 mg QD.	Metabolized by mixture of enzymes, including CYP 3A4; however, no significant change in citalopram levels when coadministered with RTV, and no dosage adjustment required.
Fluoxetine	Start at 20 mg QD; not to exceed 80 mg QD. Also available in weekly delayed release dose formulation: 90 mg once weekly commence 7 days after last daily dose of daily 20 mg formulation.	Metabolized by CYP 2D6; may increase RTV AUC by 20% but no adjustment required when coadministered with RTV.

Paroxetine	Start at 20 mg QD; may increase daily dosage by 10 mg every 7 days to maximum of 50 mg QD.	<p>DRV and FPV decrease paroxetine levels; titrate paroxetine to effect.</p> <p>Must be tapered slowly when discontinuing to avoid rebound depression symptoms and discontinuation symptoms.</p> <p>Slightly more sedating than other SSRIs.</p>
Sertraline	Start at 50 mg QD; may increase daily dosage by 25-50 mg every 7 days to maximum of 200 mg QD.	DRV decreases sertraline levels; titrate sertraline to effect.

SNRIs

- Increase presynaptic levels of serotonin and norepinephrine
- Also approved for treatment of neuropathic pain and peripheral neuropathy
- **Most common side effects:** GI events (nausea, diarrhea, constipation), dry mouth
- **Other side effects:** somnolence, insomnia, dizziness, nervousness, headache, sexual dysfunction can occur

Generic Drug Name	Usual Starting Dosage/Dosage Titration	Comments/Drug Interactions
Duloxetine	Start at 20 mg QD; may increase to BID, then to 60 mg QD or divided as 30 mg BID.	<p>Hepatically metabolized; not recommended for use in patients with hepatic impairment.</p> <p>To discontinue, taper gradually.</p>

Venlafaxine Formulations

Venlafaxine immediate release	Start at daily dosage of 75 mg divided BID (i.e., 37.5 mg BID) or TID (i.e., 25 mg TID) with food; may increase total daily dosage by up to 25 mg per dose every 4 days;	<p>Metabolized by CYP 2D6</p> <p>When stopping venlafaxine, it is essential to taper slowly to avoid discontinuation symptoms.</p> <p>Postmarketing studies suggest that venlafaxine overdoses</p>
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	maximum daily dosage: 375 mg divided TID (i.e., 125 mg TID).	are more associated with fatal outcomes than are SSRI overdoses, but less than TCA overdoses; use lowest effective dosage of venlafaxine.
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Other

Generic Drug Name	Usual Starting Dosage/Dosage Titration	Comments/Drug Interactions
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Bupropion Formulations

Bupropion	-	<p>Inhibits CYP 2D6 EFV, LPV/r, and TPV decrease bupropion levels; titrate bupropion to effect.</p> <p>Side effects: restlessness, agitation, insomnia.</p> <p>Bupropion increases seizure incidence (0.4% at 300 mg/day or higher); contraindicated in patients with elevated risk of seizures.</p> <p>Sexual dysfunction unlikely.</p>
Bupropion immediate release	Start at 75-100 mg BID for 3 days, increase to 100 mg TID on day 4; maximum daily dosage: 450 mg divided QID.	<p>No single dose should exceed 150 mg, and doses should be taken at least 6 hours apart.</p> <p>Dosage escalation should be delayed for agitation, motor restlessness, or insomnia.</p>
Bupropion SR	Start at 100-150 mg QAM; increase to usual dosage of 150 mg BID no earlier than day 4; maximum daily dosage: 400 mg divided BID (i.e., 200 mg BID).	<p>Doses of bupropion SR should be taken at least 8 hours apart.</p> <p>Dosage escalation should be delayed for agitation, motor restlessness, or insomnia.</p>

Other		
Generic Drug Name	Usual Starting Dose/Dosage Titration	Comments/Drug Interactions
Bupropion Formulations		
Bupropion XR	Start at 150 mg QAM; increase to usual dose of 300 mg QAM no earlier than day 4; maximum dosage: 450 mg QD.	Doses should be taken at least 24 hours apart. Dosage escalation should be delayed in the event of agitation, motor restlessness, or insomnia.



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PTSD and Trauma Informed HIV Care

KEY POINTS

- PTSD among people living with HIV (PLWH) is common and is associated with non-adherence to ARV and decreased virologic control.
- PTSD can result from HIV-related or unrelated trauma events.
- PTSD can be diagnosed and preliminarily treated in primary care.
- Psychotropic medications and psychotherapy are effective at treating PTSD in PLWH.
- VA has a PTSD Consultation Program for frontline VA providers working with a Veteran with PTSD, <https://www.ptsd.va.gov/professional/consult/index.asp>



BACKGROUND

- After a traumatic or life-threatening event (e.g., combat, assault, including child sexual assault, natural disaster), it is common to have reactions such as reliving the event (nightmares, intrusive memories); avoidance of situations that remind a person of the event; negative beliefs and feelings; and hypervigilance or increased startle response. However, if these symptoms do not remit or worsen after one month, a diagnosis of PTSD may be indicated per DSM-5 diagnostic criteria.
- Veterans are at increased risk for developing PTSD due to combat exposure. 11-30% of Veterans have combat-related PTSD depending on war era and deployment, with Vietnam War Veterans at highest risk for PTSD.
- Military sexual trauma is also linked to PTSD, with 55% of female and 38% of male Veterans reporting sexual harassment in the military. According to one study of female Veterans, those with MST had higher rates of PTSD compared to those with other trauma (60% versus 43%, respectively). MST was also a stronger predictor of PTSD than other traumas.
- Trauma exposure and PTSD are disproportionately higher for people living with HIV due to higher likelihood of trauma exposure in childhood (including physical and sexual abuse); repeated traumatization later in life; physical and sexual assault; and crime-related violence. Additionally, sexual and physical abuse are correlated with increased HIV risk behaviors (e.g., substance use, multiple sexual partners, commercial sex work, high risk sexual practices) and subsequent HIV infection.

Note: Some medications mentioned in this chapter may not be available on the VHA National Formulary (<https://www.pbm.va.gov/NationalFormulary.asp>). Consult VA pharmacists for alternatives.

- African Americans men who have sex with men (MSM) are disproportionately represented among new HIV infections and often experience racism-based trauma, which is also linked to greater HIV risk.
- Approximately 95% of PLWH report experiencing one lifetime trauma and 54% meet criteria for PTSD.
- Up to 40% of PLWH identify their HIV diagnosis as the traumatic event associated with the onset of their PTSD symptoms. Research has found that those with a history of PTSD are more likely to experience their HIV diagnosis as traumatic.
- Trauma exposure is associated with poorer health outcomes among PLWH, such as:
 - Higher rates of antiviral non-adherence, particularly if PTSD-related dissociative symptoms and substance use are present.
 - Decreased health-related quality of life for PLWH who reported greater HIV-related trauma symptoms.
 - Decreased virologic control (viral load >400 c/mL). One study found this was predicted by minority racial/ethnic membership, lower baseline CD4, more lifetime traumas, and more severe traumas.
 - Dysfunction and suppression of the hypothalamic-pituitary-adrenal (HPA) axis, resulting in higher cortisol levels and chronic systemic inflammation.
 - Increased likelihood of Coronary Artery Disease (CAD) for those who experienced their HIV diagnosis as traumatic.
 - More chronic pain conditions in PLWH that reported multiple traumas.
- Per the Substance Abuse and Mental Health Services Administration (SAMHSA), a trauma-informed approach consists of:
 - Realizing the impact of trauma and the potential pathways to recovery.
 - Recognizing the signs and symptoms of trauma in Veterans, their families, staff, and others involved in the health care system.
 - Responding by integrating trauma knowledge into policies, procedures, and practices.
 - Anticipating and avoiding practices that may re-traumatize Veterans (e.g., being overly authoritative or confrontational, not respecting personal space, challenging or discounting reports of abuse/trauma, labeling and pathologizing Veteran's feelings and reactions).
- A trauma-informed approach involves key principles to promote recovery and resilience from trauma:
 - Safety
 - Trustworthiness and transparency
 - Peer support

- Collaboration and mutuality
- Empowerment, voice, and choice
- Cultural, historical, and gender issues

Veterans with HIV/AIDS

- To provide trauma-informed care, clinicians know and recognize the impact of trauma on mental health and health behavior; as such, clinicians understand and are able to identify the potential relationship between trauma, HIV risk behavior (e.g., substance use, high risk sexual practices), and HIV acquisition.
- 25% of Veterans with HIV are also diagnosed with PTSD.
- Among Veterans who do not have HIV, PTSD and substance use diagnoses increased their risk of HIV infection by 12 times compared to those without PTSD and substance use diagnoses.
- Among Vietnam War Veterans with PTSD, those who used intravenous drugs were more likely to be exposed to HIV.
- Among active duty personnel, positive screens for PTSD were correlated with HIV risk behavior (unprotected anal intercourse, treatment for sexually transmitted infections, and injection drug use); HIV risk behavior was even higher for those with PTSD and major depressive disorder. This study's findings were comparable to the prevalence of HIV risk behaviors found in other trauma populations.



EVALUATION

Acute Stress Disorder and PTSD are both disorders that can arise after exposure to a traumatic event. Both Acute Stress Disorder and PTSD have similar clinical symptoms; however, Acute Stress Disorder and PTSD differ regarding the required number of symptoms and duration of symptoms. A trauma-informed approach to evaluation includes universally screening for Acute Stress Disorder and PTSD. Unrecognized and unaddressed trauma symptoms can negatively affect medical and mental health outcomes and screening for trauma can prevent misdiagnosis and inappropriate treatment planning. Therefore, clinicians should:

1. Ask all Veterans about any history of trauma.
2. Only use validated instruments for screening and assessment.
3. Screen all Veterans who have histories of trauma for other mental health disorders (e.g., anxiety-related disorders, depressive disorders) and suicidal thoughts and behaviors.

4. Be aware that some Veterans will not connect their trauma history and current behavioral patterns (e.g., substance use, avoidance, high risk sexual behaviors).
5. Do not require Veterans to describe emotionally-overwhelming trauma events in detail.
6. Focus on how trauma symptoms affect the Veteran's current functioning.
7. Inform the Veteran how you will use screening results for treatment planning to promote shared decision-making.

Effective evaluation also involves clinicians knowing the impact of trauma on physical and mental health and recognizing clinical symptoms based on DSM-5 diagnostic criteria. Furthermore, to effectively assess for clinical symptoms, clinicians develop rapport and foster a relationship of mutual trust, safety, and collaboration. Clinicians also understand historical (e.g., past history of trauma) and cultural (e.g., racial, military, socio-economic status, gender, sexual identity) factors influence conceptualization of symptoms and diagnosis.

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SCREENING

- Screening for PTSD in Primary Care is important since many people with PTSD and other mental health disorders (particularly those with stigma-related concerns) present initially in primary care settings versus specialty mental health.
- The VA recommends using the Primary Care PTSD Screen (PC-PTSD) or the PTSD Checklist (PCL) to screen for PTSD in the primary care and specialty care settings, and are validated in these contexts. The PC-PTSD and PCL are available in Mental Health Assistant in CPRS¹

The PC-PTSD and the PCL I

The PC-PTSD is a 4-question screener. If 3 of 4 items are endorsed, the PC-PTSD is considered a positive screen. If the PC-PTSD result is negative, further screening is not necessary.

If the PC-PTSD result is positive, the patient should be screened on the same day with the PCL (a 20-item questionnaire that assesses the DSM-5 PTSD criteria) with all responses and the total score recorded in the patient's chart. As an alternative, the patient can be screened with the PCL with all responses and the total score recorded in the patient's chart. An overall cutoff score of 33 on the PCL is recommended for screening.

Patients who screen positive for PTSD should be evaluated for risk factors that indicate a need for immediate intervention. Specifically, patients should be assessed for the presence of suicidal ideation and suicide risk, since PTSD is associated with increased risk for self-harm and history of suicide attempts. Providers should assess for the patient's immediate safety and determine the most appropriate treatment plan. CPRS has a detailed suicide risk assessment template. See **Depression**, p. 149. Furthermore, for patients with suspected PTSD, we recommend an appropriate diagnostic evaluation including determination of DSM criteria via a structured diagnostic interview (i.e., Clinician-Administered PTSD Scale for DSM-5; CAPS-5), functional status, medical history, past treatment history, and relevant family history.

Acceptable screening is summarized as follows:

Screening Tool Used	PC-PTSD Result	PCL Result
If PC-PTSD initially used:	And result Negative, then:	Not required
If PC-PTSD initially used:	And result Positive, then:	Required on the same day
If PCL initially used:	Not required	N/A

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- 1 There is a more recent version of the PC-PTSD, the PC-PTSD-5, which was updated in accordance with DSM-5 criteria. Compared to the PC-PTSD, the PC-PTSD-5 has 1 additional item ("In the past month, have you felt guilty or unable to stop blaming yourself or others for the event(s) or any problems the event(s) may have caused?") and is considered a positive screen if patient endorses 3 of 5 questions. At the time of this manual, the PC-PTSD-5 was not yet available in Mental Health Assistant. Also, VA and DoD are continuing to use the 4-question PC-PTSD, which is reasonable because the PC-PTSD performs well as a screen for PTSD diagnosed according to DSM-5. Research is underway to confirm the optimal cutoff point for the PC-PTSD-5.

The PC-PTSD

Have you ever had any experience that was so frightening, horrible or upsetting, that **in the past month**, you:

1. Have had any nightmares about it or thought about it when you did not want to?
Yes / No
2. Tried hard not to think about it or went out of your way to avoid situations that remind you of it?
Yes / No
3. Were constantly on guard, watchful, or easily startled?
Yes / No
4. Felt numb or detached from others, activities, or your surroundings?
Yes / No

Scoring the PC-PTSD

PC-PTSD Score	Probability of PTSD (%)
1	44
2	51
3	65
4	71

Prins et al. (2003). The primary care PTSD screen (PC-PTSD): Development and operating characteristics. *Primary Care Psychiatry*, 9(1), 9–14.

The PCL

Below is a list of problems and complaints that people sometimes have in response to stressful life experiences. Please read each one carefully, then select the appropriate number to indicate how much you have been bothered by that problem in the past month.

In the past month, how much were you bothered by:		0	1	2	3	4
		Not at all	A little bit	Moderately	Quite a bit	Extremely
1.	Repeated, disturbing, and unwanted memories of the stressful experience?	-	-	-	-	-
2.	Repeated, disturbing dreams of the stressful experience?	-	-	-	-	-
3.	Suddenly feeling or acting as if the stressful experience were actually happening again (as if you were actually back there reliving it)?	-	-	-	-	-
4.	Feeling very upset when something reminded you of the stressful experience?	-	-	-	-	-
5.	Having strong physical reactions when something reminded you of the stressful experience (for example, heart pounding, trouble breathing, sweating)?	-	-	-	-	-
6.	Avoiding memories, thoughts, or feelings related to the stressful experience?	-	-	-	-	-
7.	Avoiding external reminders of the stressful experience (for example, people, places, conversations, activities, objects, or situations)?	-	-	-	-	-
8.	Trouble remembering important parts of the stressful experience?	-	-	-	-	-
9.	as: I am bad, there is something seriously wrong with me, no one can be trusted, the world is completely dangerous)?	-	-	-	-	-
10.	Blaming yourself or someone else for the stressful experience or what happened after it?	-	-	-	-	-

In the past month, how much were you both experienced by:	0 Not at all	1 A little bit	2 Moderately	3 Quite a bit	4 Extremely
11. Having strong negative feelings such as fear, horror, anger, guilt, or shame?	-	-	-	-	-
12. Loss of interest in activities that you used to enjoy?	-	-	-	-	-
13. Feeling distant or cut off from other people?	-	-	-	-	-
14. Trouble experiencing positive feelings (for example, being unable to feel happiness or have loving feelings for people close to you)?	-	-	-	-	-
15. Irritable behavior, angry outbursts, or active aggressiveness?	-	-	-	-	-
16. Taking too many risks or doing things that could cause you harm?	-	-	-	-	-
17. Being “super alert” or watchful or on guard?	-	-	-	-	-
18. Feeling jumpy or easily startled?	-	-	-	-	-
19. Having difficulty concentrating?	-	-	-	-	-
20. Trouble falling or staying asleep?	-	-	-	-	-

Scoring the PCL

PCL Score	Qualitative Description
Lower than 33	Patient does not meet criteria for PTSD
33 or higher	Patient meets criteria for PTSD and may benefit additional assessment and treatment for PTSD

As with all self-report questionnaires, assessment results should be interpreted and guided by clinical experience.

PTSD Symptoms may be Associated with Conditions Other than PTSD

Given the overlap between PTSD symptoms and symptoms of other illnesses or disorders, the following should be considered when patients with HIV present with PTSD symptoms.

Screening	<ul style="list-style-type: none"> • PC-PTSD (see above) • PCL (see above)
History	<ul style="list-style-type: none"> • Relationship between the onset of PTSD symptoms and trauma/stressors • Differentiating between PTSD symptoms related to HIV or another trauma/stressor • Concurrent medical disease • Use of alcohol or illegal/legal substances • Past history of PTSD or trauma • Family history of mental illness
Differential Diagnosis	<ul style="list-style-type: none"> • Other Trauma- and Stressor-related Disorders (e.g., Acute Stress Disorder, Adjustment Disorder) • Obsessive-compulsive Disorder • Anxiety Disorders (e.g., Panic Disorder, Generalized Anxiety Disorder) • Mood Disorders (e.g., Major Depression, Bipolar Disorder) • Personality Disorders • Conversion Disorder • Psychotic Disorders • Traumatic Brain Injury and other Cognitive Disorders • Alcohol or Drug Use/abuse • Sleep Disturbance

Special Considerations for Veterans with HIV and PTSD

Veterans with HIV, whether they have been diagnosed with PTSD or not, have likely experienced trauma in their lives. As clinicians, caring for any Veteran in the VA healthcare system, trauma should be in the back of our minds. Veterans with HIV and comorbid PTSD and other mental health or substance use disorders often experience stigma and discrimination, which can sometimes be subtle. Stigma includes feeling that you will be judged, discriminated, or stereotyped because of a condition. As with many people, Veterans may want to avoid talking about PTSD, mental health, or substance use problems. For some Veterans, Primary Care may be the first place they disclose or share their trauma or PTSD symptoms.

Trauma Informed Care for Veterans with HIV

The following key principles clinicians are recommended to ensure a trauma-informed approach for Veterans who have a history of trauma and HIV.

Establish Safety:

- Demonstrate respect and professionalism.
- Review confidentiality, particularly regarding how information about trauma and HIV will be used.
- Establish specific routines, as a structured setting can provide a sense of safety and familiarity.
- Ask about trauma, HIV, and topics involving sex. Bringing up these issues may feel taboo or intrusive. However, asking in a supportive, caring way gives Veterans permission to talk about these issues that they may not feel comfortable with raising on their own. This helps promote safety and trust. It can also be helpful to inform Veterans that everyone is asked these questions. Also, provide Veterans with a rationale for why they are being asked.
- To minimize and prevent further stigmatization, clinicians should avoid labeling HIV-positive Veterans or assuming stereotypes (e.g., they are gay, MSM, sex workers, injection drug users, promiscuous) and should use person-first language (e.g., Veteran with HIV rather than an HIV/AIDS patient, Veteran with substance use disorder rather than substance user, lesbian/gay/bisexual/transgender Veteran rather than a gay, a lesbian, a bisexual, or a transgender.)

Prevent Re-traumatization:

- Be aware and sensitive to the needs of Veterans with trauma histories and HIV. Consider the behaviors or stimuli in the treatment setting that may trigger traumatic memories.
 - For example, the following may be triggering depending on the trauma: small enclosed spaces, abrupt loud noises, clinician demo-

graphics (e.g., race, ethnicity, age, gender, sexual orientation) if pertinent to the trauma (e.g., a female Veteran with a history of MST by male superiors may prefer female providers).

- Some Veterans may find the word “HIV” triggering. As such, clinicians should find emotionally neutral terms to discuss HIV.
- Clinicians should assist Veterans in finding a provider of their gender preference.
- Routine gynecological/prostate exams may re-traumatize Veterans; thus, mental health can be involved for consultation as well as Veteran support or emotional assistance.
- Clinicians should also take symptoms and reports of trauma seriously. Ignoring, questioning, or challenging these may be invalidating and reinforce shame, avoidance, and helplessness, particularly if their reports previously went ignored.
- Veterans should not be required to describe trauma details that are emotionally-overwhelming.
- Trustworthiness and Transparency:
 - Be clear and honest with treatment plans, boundaries, and obligations.
 - Be dependable and consistent. Follow through with the treatment plan and the Veteran’s requests.

Peer Support:

- Encourage Veterans to seek social support from family, friends, and other Veterans.
- Peer support and social interactions with similar others are particularly important since many Veterans with trauma and HIV often feel marginalized, stigmatized, and alone in their experience.
- Peer support allows Veterans to form mutual relationships, to move beyond trauma and HIV, and to mirror and to learn alternative, adaptive coping strategies and to promote resiliency to trauma and HIV.

Collaboration and Mutuality:

- Ask permission from the Veteran to talk about potentially sensitive or difficult topics.
- Use a patient-centered style of communication by asking open-ended questions with a focus on eliciting the Veteran’s self-identified symptoms, problems, and treatment goals.
- Provide affirmations about progress made toward goals or overcoming barriers (e.g., behavior change, medication adherence, adaptive coping, decreasing avoidance).
- Reflect back to the Veteran what they are communicating to demonstrate active listening and to verify your understanding of what the Veteran is sharing.

Empowerment, Voice, and Choice:

- Provide Veterans with a sense of control and help them feel empowered to make their own decisions.
- Assist with basic and social needs by making referral to Social Work for resources such as housing, shelters (especially for female Veterans and their children), employment, transportation, etc.
- Educate about common symptoms, reactions, and consequences of trauma and HIV. Education can help normalize symptoms, correct misinformation and myths related to trauma and HIV, and provide relief to Veterans who feel they are alone in their struggle.
- Inform about resources (e.g., mental health treatment, educational handouts, peer support groups, medications, medical treatment options).
- Build hope and resilience. Focus on the Veteran's strengths, positive attributes, and positive resources. Emphasize the Veteran's past ability to cope with hardship and to overcome adversity, also assure them that PTSD and HIV are both treatable and manageable conditions. Help the Veteran find meaning and recovery from their HIV narratives to work towards post-traumatic growth.

Cultural and Historical Issues:

- Determine if a Veteran has experienced multiple traumas or a single trauma, since research shows those with multiple traumas are most susceptible to severe traumatic responses.
- Determine the context of how the Veteran contracted and was diagnosed with, as these events may involve a traumatic event.
- Define how culture affects how a Veteran organizes information, interprets, and resolves their trauma and HIV status.
- Identify people who know about a specific cultural factor and can help interpret cultural patterns and serve as liaisons (e.g., if working with a gay or bisexual male Veteran, find a peer support specialist who is also a sexual minority and familiar with the military culture and history of oppression around LGBT issues).
- Determine how a Veteran's social support network views and reacts to the trauma and HIV.

Psychotherapy and Other PTSD Treatment Options

Evidence-based psychotherapy is the primary intervention for PTSD. Clinicians are encouraged to be familiar with these treatments to effectively educate patients about PTSD treatment options and to assist in shared decision-making regarding treatment options, all of which are principles of a trauma informed approach.

There are various trauma-focused psychotherapies that are evidence-based and help people make sense of the trauma; learn to better handle negative thoughts

and feelings; reconnect with loved ones; and set treatment goals. The psychotherapies with the strongest evidence from clinical trials include:

- Cognitive Processing Therapy (CPT) is an intervention whereby patients learn skills to understand how trauma has changed their thoughts and feelings. Changing how patients think about the trauma therefore helps change how patients feel about the trauma.
- Prolonged Exposure (PE) is an intervention whereby patients repeatedly talk about the trauma until the memories are no longer distressing. This helps the patient achieve a sense of control over their thoughts and feelings about trauma. PE also helps patients return to places or do things that are safe that they previously avoided because they reminded them of the trauma.
- Eye Movement Desensitization and Reprocessing (EMDR) is a trauma-focused psychotherapy that helps patients process upsetting memories, thoughts, and feelings related to trauma. Of note, EMDR is different than CPT and PE because it involves paying attention to back-and-forth movement or sound while recalling the upsetting memories with the aim of making memories less distressing.

Other treatment recommendations include:

- Psychotherapy for insomnia (Cognitive Behavior Therapy – Insomnia, or CBTi) is also recommended for managing sleep difficulties related to PTSD. Often, patients with PTSD experience PTSD-related nightmares.
- PTSD Recovery/Support Groups available in Primary Care
- To promote Veteran empowerment and choice, consistent with a trauma-informed approach, there are also self-help tools developed by the VA for Veterans, including the PTSD Coach Mobile App and the Mindfulness Coach App. These are apps that can be downloaded to a smartphone for Veterans to use.
 - The PTSD Coach app provides facts about PTSD and research-based self-help skills (for example, tools for screening and tracking symptoms, stress management skills). We recommend Veterans use the PTSD Coach app with professional medical treatment.
 - The Mindfulness Coach app provides education about mindfulness and its benefits for coping with negative thoughts and emotions. It also provides reminders and tools to practice and track progress.
- Consistent with the peer support principle of trauma informed care, most VAs offer peer support mentorship, often from another Veteran who is diagnosed with and treated for PTSD. This can help the Veteran with trust and potentially overcoming barriers of avoidance and stigma.

Trauma-focused psychotherapy for people living with or at risk for HIV:

- Trauma-focused psychotherapy decreases HIV risk behavior (i.e., unprotected sex).

- PTSD treatment in patients who are HIV-positive is associated with greater adaptive coping, decreased trauma-related symptoms (i.e., intrusive and avoidance symptom) and decreased substance use); however, findings are mixed and warrant additional future research on this topic.
- There is a paucity of research regarding the effects of PTSD treatment on HIV medical outcomes; however, studies find that cognitive behavioral therapy for people living with HIV was effective in enhancing adherence, increasing CD4-cell counts, and reducing depressive symptomatology.



WHEN TO REFER

Indications for referring patients with PTSD to a mental health provider:

- Suicidal thought with plan or intent.
- Symptoms that are disabling or significantly disrupting a patient's life (e.g., work, relationships, daily functioning).
- If symptoms persist after several months following the trauma or worsen over time.
- Pronounced affective instability.



MANAGEMENT

Patients diagnosed with PTSD who choose not to engage in, are unable to access trauma-focused psychotherapy, or require additional treatment may benefit from pharmacotherapy. Sertraline, paroxetine, fluoxetine, and venlafaxine are all appropriate agents to be used as monotherapy according to the most recent 2017 VA/DoD Clinical Practice Guidelines for the Management of Posttraumatic Stress Disorder (PTSD) and Acute Stress Disorder. The following medications (see below) used for PTSD are either “recommended for” or “suggested for” by the 2017 PTSD guidelines. All antidepressants have a Black Box Warning that warns of a possible increased risk of suicidal thoughts and behavior in children, adolescents, and young adults. These risks, however, are not increased beyond the age of 24 and may decrease in adults aged 65 and older.

Sertraline, paroxetine, and fluoxetine are in the antidepressant class of Selective Serotonin Reuptake Inhibitors (SSRIs). This class of medications, although relatively safe, may interact with antiretroviral medications. Because of the potential for interactions, careful dose titration of the SSRI to the desired effect is recommended using the lowest feasible SSRI dose and monitoring for antidepressant effect. Venlafaxine is in the antidepressant class of Serotonin Norepinephrine Reuptake Inhibitors (SNRIs). Venlafaxine is a substrate of CYP 3A4 and subject to many drug-drug interactions if co-administered with a strong CYP 3A4 inhibitor or inducer. Both fluoxetine and venlafaxine have QT-prolongation effects which may be worsened when used with other ARV therapies that increase the risk.

According to the VA/DoD PTSD guidelines, nefazodone, imipramine, and phenelzine are also recommended as monotherapy if recommended pharmacotherapy is ineffective, unavailable, or not in accordance with patient preference or tolerance. However, it is important to note that both nefazodone and phenelzine have serious potential toxicities, including hypertensive crisis for phenelzine and liver failure for nefazodone, which both may lead to death.

! POTENTIAL ARV INTERACTIONS

PTSD and Associated Trauma

Medication	Antiretroviral	Interaction
Sertraline	<ul style="list-style-type: none"> • Darunavir/ritonavir • Darunavir/cobicistat • Lopinavir/ritonavir • Atazanair/cobicistat 	<p>Sertraline AUC decreased by 49% with darunavir/ritonavir; titrate sertraline dose to clinical response</p> <ul style="list-style-type: none"> • SSRIs are CYP 2D6 inhibitors and may ↑ CYP 2D6 substrate exposure (i.e. ritonavir) and risk of toxicity • Careful dose titration of SSRI to desired effect using lowest feasible dose and monitoring for antidepressant effect
Paroxetine	<ul style="list-style-type: none"> • Darunavir/ritonavir • Darunavir/cobicistat • Atazanair/cobicistat • Tipranavir • Lopinavir/ritonavir 	<ul style="list-style-type: none"> • Paroxetine AUC decreased by 39% with darunavir/ritonavir; titrate paroxetine dose to clinical response • Tipranavir and lopinavir/ritonavir may ↑ paroxetine levels • SSRIs are CYP 2D6 inhibitors and may ↑ CYP 2D6 substrate exposure (i.e. ritonavir) and risk of toxicity • Careful dose titration of SSRI to desired effect using lowest feasible dose and monitoring for antidepressant effect
Fluoxetine	<ul style="list-style-type: none"> • Atazanavir/cobicistat • Efavirenz • Atazanair/cobicistat • Darunavir/cobicistat 	<ul style="list-style-type: none"> • The combination of the following medications with fluoxetine can potentially ↑ the risk of QT-interval prolongation; consider an alternative agent to avoid toxicity

Medication	Antiretroviral	Interaction
-	-	<ul style="list-style-type: none"> • SSRIs are CYP 2D6 inhibitors and may ↑CYP 2D6 substrate exposure (i.e. ritonavir) and risk of toxicity • Careful dose titration of SSRI to desired effect using lowest feasible dose and monitoring for antidepressant effect
Venlafaxine	<ul style="list-style-type: none"> • Atazanavir • Darunavir • Ritonavir 	<ul style="list-style-type: none"> • These ARVs are CYP 3A4 inhibitors. Concomitant use with venlafaxine, a substrate of CYP 3A4, may result in ↑ venlafaxine plasma concentrations and toxicity; Consider therapy modification or carefully titrate dose of venlafaxine to desired effect using lowest feasible dose and monitoring for antidepressant effect
Nefazodone	<ul style="list-style-type: none"> • Pls • Ritonavir • Maraviroc 	<ul style="list-style-type: none"> • Nefazodone, a strong CYP3A4 inhibitor, may ↑ exposure of maraviroc. Use is contraindicated in patients with severe renal impairment • Consider alternatives to, or reduced doses of, nefazodone in patients treated with Pls • Nefazodone, a strong CYP3A4 inhibitor, may ↑ exposure of maraviroc. Use is contraindicated in patients with severe renal impairment
Imipramine	<ul style="list-style-type: none"> • Atazanavir • Ritonavir • Darunavir • Tipranavir 	<ul style="list-style-type: none"> • The combination atazanavir with imipramine should be avoided due to the increased risk of QT-prolongation • Use with atazanavir or darunavir may increase plasma concentrations of imipramine leading to potential toxicity; Consider therapy modification
Phenelzine	No contraindications or major drug-drug interactions with antiretroviral agents	

Medication	Antiretroviral	Interaction
Prazosin	No contraindications or major drug-drug interactions with antiretroviral agents	



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Serious Mental Illness (Bipolar Disorder, Schizophrenia, etc.)

KEY POINTS

- Individuals with serious mental illness (SMI) are at increased risk of contracting and transmitting HIV.
- SMI among HIV-infected persons is associated with high-risk behavior, nonadherence to ARV therapy, and all-cause mortality.
- Psychotropic medication and psychotherapy are effective for treating SMI; treatment may reduce high-risk behavior and may improve adherence to ARV therapy in HIV-infected persons.
- Progression of HIV to AIDS can produce symptoms of mania and psychosis.



BACKGROUND

The category of SMI includes mood disorders, such as bipolar I and II, and psychotic disorders, such as schizophrenia, that significantly impair functioning.

Prevalence estimates of HIV within the SMI population are much higher (4-23%) than the general population (0.5%).

Individuals with SMI are more likely to engage in high-risk sexual behaviors, such as having unprotected sex, having multiple sex partners, and commercial sex work. They are also significantly more likely to be the victims of sexual violence and more likely to have sexually transmitted diseases (STDs).

Mental health symptoms in SMI such as impulsivity, hypersexuality, cognitive impairment, low self-esteem, and social skill deficits contribute to risky sexual behavior. Persons with SMI are also more likely to be of low socioeconomic status, live in ultra urban areas, and spend time in institutions (e.g., hospitals, jail). Consequently, they may not have access to condoms (e.g., due to cost or availability in institutions) and yet often live in urban cores that have high rates of STDs and HIV.

Co-occurrence of substance use disorders is common in persons with SMI. Dual diagnosis is linked to more sexual risk behavior, as well as increased risk of HIV infection and mortality.

Comorbidity of SMI and HIV is associated with poor adherence to ARV therapy and psychotropic medications, as well as poorer health outcomes in general.

Note: Some medications mentioned in this chapter may not be available on the VHA National Formulary (<https://www.pbm.va.gov/NationalFormulary.asp>). Consult VA pharmacists for alternatives.

Veterans with SMI

- Approximately 15% of Veterans have SMI, with schizophrenia occurring in about 3% and bipolar disorder in about 2% of Veterans.
- Veterans with SMI are up to 2 times more likely to have HIV than those without SMI.
- Veterans with SMI are more likely to develop chronic medical conditions and are at particularly high risk for cardiac disease.
- Veterans with SMI have 1.32 to 1.55 times greater risk of all-cause mortality.



WHEN TO REFER

SMI typically requires ongoing medication management by a mental health care provider. Indications for referral to address acute issues include:

- Suicidal thought with plan or intent
- Pronounced affective instability
- Active psychotic symptoms (e.g., hallucinations, delusions)
- Increased impulsive and risky behavior
- Significant functional impairment (e.g., in work, school, relationships, or self-care)



EVALUATION

Bipolar Disorder

Characterized by manic (bipolar I) or hypomanic (bipolar II) episodes and major depressive episodes

Manic Episode	Persistent elevated or irritable mood and increased activity or energy lasting at least 1 week and at least 3 of the following during same period: <ol style="list-style-type: none">1. Inflated self-esteem or grandiosity2. Decreased need for sleep3. Hyper-talkative or pressured speech4. Racing thoughts5. Distractibility6. Increased goal-directed activity (social, work, sexual) or psychomotor agitation7. Increased risky behavior (e.g., buying sprees, foolish business investments, promiscuity unusual for the individual)
Hypomanic Episode	Criteria as in manic episode, lasting at least 4 days

Schizophrenia

Characterized by positive symptoms, negative symptoms, and cognitive symptoms (e.g., working memory and attention problems)

Presence of symptoms for at least 6 months with at least 2 symptoms present for a significant portion of time in a 1-month period

Positive Symptoms	<p>Must have at least 1 of the first 3 positive symptoms:</p> <ol style="list-style-type: none"> 1. Delusions 2. Hallucinations 3. Disorganized speech 4. Disorganized behavior
Negative symptoms	<ol style="list-style-type: none"> 1. Catatonic behavior (e.g., stupor, catalepsy, mutism, waxy flexibility, stereotypy, echolalia, echopraxia, negativism, posturing, grimacing) 2. Avolition 3. Flat affect

Other psychotic disorders include: *delusional disorder*, in which delusions are the most prominent symptom and other symptoms (including hallucinations) are typically absent; *schizoaffective disorder*, with concurrent positive symptoms of schizophrenia and a major mood episode; *brief psychotic disorder*, with schizophrenia symptoms lasting less than 1 month; and *schizophreniform disorder*, with schizophrenia symptoms lasting between 1 and 6 months.

Manic and psychotic symptoms may be associated with illnesses other than SMI

The onset of SMI typically occurs in late adolescence to early adulthood (16-35 years of age). First presentation of manic or psychotic symptoms in middle aged and older adults may be associated with an illness other than SMI. Potentially treatable or reversible causes of these symptoms (see list below) should be considered when persons with HIV present with manic or psychotic symptoms.

Factors to Consider	<ul style="list-style-type: none"> • Age of first symptom onset • Past history of depression and SMI • Concurrent chronic disease • Medication history, including recent changes • Use of alcohol or other psychoactive drugs, whether legal or illegal • Suicidal thoughts • Family history of mental illness
Laboratory studies	<ul style="list-style-type: none"> • RPR • TSH • ACTH (for Cushing's disease) • B12

	<ul style="list-style-type: none"> • PBG and ALA (for AIP)
Differential Diagnosis	<ul style="list-style-type: none"> • Acute intermittent porphyria (AIP) • CNS infections • CNS neoplasms • Cushing's disease • Delirium • Dementia • Drug use • Drug effects or side effects • HIV-related mania or psychosis (see section below) • Hyperthyroidism • Hypothyroidism

HIV-related Mania and Psychosis

Mania

Rates of manic episodes in early HIV infection are only slightly higher than the general population at 1-2%; however, 4-8% of individuals with AIDS exhibit mania. AIDS-related mania is secondary to HIV infection of the central nervous system and tends to be associated with dementia and cognitive slowing. It may occur in those without a personal or family history of mood disorders and differs from typical bipolar mania in that symptoms tend to be more severe and chronic in nature. Additionally, those with AIDS mania are more likely to experience irritability rather than euphoria, and are less likely to be hyper-talkative.

Psychosis

Prevalence estimates of new onset psychosis in persons with HIV range from 0.23-15.2%. New onset psychosis typically occurs in the context of AIDS or in later stages of HIV infection. AIDS-related dementia, opportunistic infection, substance dependence, and ARV therapy toxicity (especially with efavirenz, but also nevirapine and zidovudine) have been implicated in new onset psychosis. Paranoid delusions and hallucinations are the most common symptoms, whereas bizarre delusions are less common than in schizophrenia. Psychosis in persons with HIV is more variable in course and more likely to remit fully over time. Importantly, lower dosage, shorter duration of antipsychotic medications is recommended for HIV-related psychosis than for schizophrenia.

Psychosocial Interventions

Psychosocial interventions for persons with SMI and HIV (or risk of HIV) address three main targets:

1) Behavioral risk reduction

These interventions decrease risk of infection (in uninfected persons) and transmission (in infected persons) by reducing risky sexual behavior. Effective interventions for persons with SMI provide information, increase motivation to engage in safe sex practices, and address skills for condom-use and communication. Interventions may also address risk due to injection drug use in a similar manner.

2) Increased medication adherence

Reasons for medication non-adherence vary by patient and a root cause analysis is important to understand why a patient is non-adherent to ARV therapy and/or psychotropic medication. Factors targeted to improve adherence include education, increased collaboration between clinician and patient, motivational interviewing to reduce ambivalence about taking medications, and reminders provided through environmental cues, social support, and/or technological support.

3) Reducing SMI symptoms and improving functioning

Managing symptoms of SMI may decrease risk behavior and improve medication adherence, in addition to improving quality of life. Monitoring and care coordination appear to be particularly important for SMI. Effective interventions for individuals with schizophrenia and bipolar disorder (see examples in table below) reduce relapse and re-hospitalization rates and improve psychosocial and occupational functioning.

Cognitive Behavioral Therapy	Identifies triggers of negative or delusional thoughts; challenges inaccurate beliefs; teaches more effective coping strategies
Family-focused interventions	Develop a collaborative relationship; provide psychoeducation, communication skills, and problem-solving skills to caregivers
Cognitive/Functional Remediation	Teach strategies that target attention, memory, organization, problem-solving, and reasoning; practice with various exercises
Social Skills Training	Involves role modeling and behavioral rehearsal, combined with positive reinforcement and corrective feedback
Interpersonal and Social Rhythm Therapy	Teaches problem-solving skills to help maintain daily routines and sleep-wake cycles

Rx MANAGEMENT

The treatment of Bipolar Disorder is directed to each subtype (type I vs. type II) for mood stabilization as well as targeted control of behavioral symptoms including reducing agitation, aggression, and impulsivity. The first line pharmacotherapy options for Bipolar Type I Disorder typically include lithium, valproate, or a second generation antipsychotic (SGA). Since lithium

is predominately metabolized by the kidneys and excreted unchanged in the urine, it is least likely to have specific cytochrome P450 (CYP) drug interactions with ARV therapy. Patients with manic and mixed episodes of depression may require treatment of valproic acid, carbamazepine, oxcarbazepine, or a SGA. Both carbamazepine and oxcarbazepine are potent CYP 3A4 inducers and interact with many ARV therapies that are metabolized through the CYP 3A4 pathway including protease inhibitors (PI) and Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTI).

For those patients with acute depressive episodes in Bipolar Type II Disorder, first line pharmacotherapy options include lithium, lamotrigine, and SGAs. Patients with HIV and a comorbid psychiatric disorder are at an increased risk for suicide. All antiepileptic drugs (AED) used for bipolar disorder including carbamazepine, oxcarbazepine, lamotrigine, and valproic acid may potentially increase the risk of suicidal thoughts and behavior. Therefore, patients who are receiving any AEDs should be monitored for worsening of depression, suicidal thoughts or behaviors, and/or any unusual changes in mood or behavior.

Schizophrenia is a lifelong illness that routinely requires pharmacological intervention in addition to cognitive and behavioral care. Antipsychotics are first line agents used for acute and maintenance treatment for patients diagnosed with Schizophrenia and/or Psychosis. Antipsychotics are separated into first and second generations. Both classes are associated with a number of side-effects including anticholinergic side effects, extrapyramidal symptoms, alterations in plasma glucose, weight gain, dyslipidemia, sexual dysfunction, and the risk for neuroleptic malignant syndrome which although rare can be life threatening. The first generation antipsychotics have historically fallen out of favor as first line agents due to higher propensity for extrapyramidal symptoms (EPS), QT-interval prolongation, and tardive dyskinesia. Second generation antipsychotics are commonly used as first line agents for the treatment of Schizophrenia and Psychosis, however, these agents have a higher risk for metabolic related side-effects. Some second generation antipsychotics, are similar to first generation antipsychotics (i.e. thioridazine, chlorpromazine, haloperidol, fluphenazine, and perphenazine) in that some of the agents are associated with QT-interval prolongation. Individuals with a previous cardiac history should avoid combinations listed below.

! POTENTIAL ARV INTERACTIONS

Bipolar Disorder

Medication	Antiretroviral	Interaction
Valproic Acid	<ul style="list-style-type: none"> • Lopinavir/ritonavir • Tipranavir 	<ul style="list-style-type: none"> • Concurrent use of valproic acid with medications may result in ↓ valproic acid serum concentrations and decreased efficacy • Consider an alternative mood stabilizer if antiretrovirals are indicated

Medication	Antiretroviral	Interaction
Carbamazepine	<ul style="list-style-type: none"> • NNRTI class • PI class • Dolutegravir • Elvitegravir • Cobicistat • Tenofovir • Maraviroc 	<ul style="list-style-type: none"> • Carbamazepine is a strong CYP 3A4 inducer • Coadministration of carbamazepine with antiretrovirals metabolized by CYP 3A4 may ↓ the antiretroviral exposure and therapeutic effect which can lead to the development of antiretroviral resistance • Consider an alternative mood stabilizer if antiretrovirals are indicated
Oxcarbazepine	<ul style="list-style-type: none"> • Rilpivirine • Darunavir • Tenofovir • Dolutegravir • Elvitegravir • Cobicistat 	<ul style="list-style-type: none"> • Oxcarbazepine is a CYP 3A4 inducer • Coadministration of oxcarbazepine with antiretrovirals that are metabolized by CYP 3A4 may ↓ the antiretroviral exposure and therapeutic effect which can lead to the development of antiretroviral resistance • Consider an alternative mood stabilizer if antiretrovirals are indicated
Lamotrigine	<ul style="list-style-type: none"> • Atazanavir • Lopinavir/ritonavir 	<ul style="list-style-type: none"> • Coadministration of lamotrigine with agents may result in ↓ lamotrigine serum concentrations • Doses of lamotrigine may need to be increased if medications are indicated • Consider an alternative mood stabilizer if antiretrovirals are indicated
Lithium	No contraindications or major drug-drug interactions with ARV therapy	

Schizophrenia/Psychosis

Medication	Antiretroviral	Interaction
Clozapine	<ul style="list-style-type: none"> • Saquinavir • Nelfinavir • Atazanavir • Efavirenz • Lopinavir/ritonavir 	<ul style="list-style-type: none"> • Clozapine may prolong the QT-interval and should be avoided with agents that also increase the risk • Consider alternative therapy

Medication	Antiretroviral	Interaction
Olanzapine	<ul style="list-style-type: none"> • Saquinavir • Fosamprenavir • Efavirenz • Lopinavir/ritonavir 	<ul style="list-style-type: none"> • Olanzapine may prolong the QT-interval and should be avoided with agents that also increase the risk • Consider alternative therapy
Quetiapine	<ul style="list-style-type: none"> • Saquinavir • Atazanavir • Cobicistat • Darunavir • Efavirenz • Indinavir • Lopinavir/ritonavir • Nelfinavir 	<ul style="list-style-type: none"> • Quetiapine may prolong the QT-interval and should be avoided with agents that also increase the risk • Quetiapine is a CYP3A4 substrate. Use with strong CYP3A4 inhibitors such as cobicistat, indinavir, or darunavir may result in ↑quetiapine exposure and toxicity • Consider alternative therapy
Lurasidone	<ul style="list-style-type: none"> • PI class • Cobicistat • Fosamprenavir • Delaviridine 	<ul style="list-style-type: none"> • Lurasidone is a CYP3A4 substrate. Concurrent use with a strong CYP3A4 inhibitor may result in ↑ lurasidone exposure and toxicity • Use with PIs and cobicistat is contraindicated • Consider alternative therapy
Risperidone	<ul style="list-style-type: none"> • Saquinavir • Efavirenz 	<ul style="list-style-type: none"> • Concurrent use of risperidone and agents may result in increased risk of QT-prolongation • Consider alternative therapy
Ziprasidone	<ul style="list-style-type: none"> • Atazanavir • Efavirenz • Lopinavir/ritonavir • Nelfinavir • Saquinavir 	<ul style="list-style-type: none"> • Ziprasidone may prolong the QT interval and should be avoided with agents that also increase the risk • Consider alternative therapy
Aripiprazole	<ul style="list-style-type: none"> • Saquinavir • Efavirenz • Atazanavir • Indinavir • Lopinavir/ritonavir • Rilpivirine • Nelfinavir • Cobicistat 	<ul style="list-style-type: none"> • Aripiprazole may prolong the QT interval and should be avoided with agents that also increase the risk • Concomitant use with agents is contraindicated • Consider alternative therapy

Medication	Antiretroviral	Interaction
First Generation Antipsychotics (thioridazine, chlorpromazine, haloperidol, etc.)	<ul style="list-style-type: none"> • PI class • Efavirenz 	<ul style="list-style-type: none"> • All first generation antipsychotics have the risk of prolonging the QT-interval and should be avoided with antiretroviral medications that can also increase the risk • Consider alternative therapy

Condom Access

One step that all VA providers can take is prescribing condoms. As mentioned above, despite being at increased risk for HIV/AIDS, there are multiple specific factors that decrease the likelihood that these individuals will be able to use condoms. VA prescribers (e.g., physicians, nurse practitioners, physician assistants) can officially prescribe condoms through CPRS and these are filled at no cost to the Veteran through the VA pharmacy. They are ordered formally (just like an Rx; in many VAs, they are found here: Orders→Meds by Drug Name→condom, miscellaneous) as a means of helping the VA account for the demand and use of this resource. Taking this step not only provides free condoms to these Veterans, it also communicates to them the importance of using protection and offers a way for providers to bring up this topic at every encounter. Condoms can also be placed in restrooms, waiting rooms, and other areas to ensure that they are freely available to all individuals.



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Health Management for People Living with HIV

Cancer Screening

KEY POINTS

- General recommendations from the United States Preventive Services Task Force (USPSTF) regarding cancer screening include the following:
 - Men and women at average risk should be screened for **colorectal carcinoma** (CRC) starting at age 50, using high sensitivity guaiac based fecal occult blood testing (gFOBT), fecal immunochemical tests (FITs), flexible sigmoidoscopy with or without FIT, or colonoscopy. Office-based digital rectal examination (DRE) plus FOBT should not be used.
 - Women aged 50 and older at average risk should be screened every 1-2 years for **breast cancer** using mammography.
 - Screening women ages 21 to 65 years every 3 years with cytology provides a reasonable balance between benefits and harms.
 - Do not use prostate-specific antigen (PSA)-based screening for prostate cancer. Contemporary recommendations for prostate cancer screening all incorporate the measurement of serum PSA levels; other methods of detection, such as digital rectal examination or ultrasonography, may be included.

There is convincing evidence that PSA-based screening programs result in the detection of many cases of asymptomatic prostate cancer, and that a substantial percentage of men who have asymptomatic cancer detected by PSA screening have a tumor that either will not progress or will progress so slowly that it would have remained asymptomatic for the man's lifetime (i.e., PSA-based screening results in considerable overdiagnosis).

- These recommendations may be applied to HIV-infected patients with CD4 counts of >350 cells/ μ L or completely suppressed HIV viral load. For patients with lower CD4 counts, screening should be discussed in the context of the patient's prognosis, preferences, and health goals.



BACKGROUND

- Patients infected with HIV are at higher risk than HIV-uninfected patients of developing AIDS-defining cancers as well as many non-AIDS-defining cancers (NADC), despite the effective use of antiretroviral therapy. HIV infection is particularly associated with a higher incidence of cancers attributable to an infectious etiology (e.g., Hodgkin lymphoma, hepatocellular carcinoma, anal carcinoma) as well as cancers associated with cigarette smoking (lung, kidney, and laryngeal). Individuals with HIV have a higher death rate attributable to many NADC than their HIV-uninfected counterparts.

Cancers occurring at a higher rate in the HIV-infected population include the following:

Note: Some medications mentioned in this chapter may not be available on the VHA National Formulary (<https://www.pbm.va.gov/NationalFormulary.asp>). Consult VA pharmacists for alternatives.

AIDS-Defining Cancers

Non-AIDS-Defining Cancers

- Kaposi sarcoma
- Cervical carcinoma
- Non-Hodgkin lymphoma (including primary CNS lymphoma, and primary effusion lymphoma)

- Anal squamous cell carcinoma (SCC)
- Colorectal carcinoma
- Lung cancer
- Skin cancer, including melanoma
- Oropharyngeal cancer
- Vaginal cancer
- Hodgkin lymphoma
- Hepatocellular carcinoma

*HIV-infected patients with chronic HBV or HCV infection may be at much higher risk of developing hepatocellular carcinoma than those without HIV coinfection. See **Cirrhosis**, p. 343.*

- Although the rates of many NADC are higher in individuals with HIV, in general, screening recommendations for most cancers are the same as for HIV-uninfected individuals, as outlined by the USPSTF. However, physicians may need to tailor their recommendations based on individual patient risk factors and in situations where no guidelines exist for screening (such as screening for anal SCC).
- Of the cancers on this list, the USPSTF has issued screening recommendations regarding cervical and colorectal cancers, which are presented in this chapter. In addition, this chapter includes USPSTF recommendations on screening for breast cancer and prostate cancer. Additional screening recommendations can be found in other chapters. See **Anal Dysplasia**, p. 315; **Cirrhosis**, p. 343; **Gastroesophageal Reflux Disease (GERD)**, p. 431, and **Women's Health**, p. 283.
- Because most cancer screening requires a 5- to 10-year life expectancy to show a favorable cost/benefit ratio, it is reasonable to screen patients who are HIV-infected for cancer if they have a CD4 count of >350 cells/ μ L or a suppressed viral load. Screening patients with more advanced HIV disease is unlikely on average to extend life expectancy or be cost-effective, and should be discussed with patients in the context of their prognosis, preferences, and health goals. However, screening for cervical carcinoma is recommended for all women with HIV, regardless of CD4 count.
- For cancers in which there is a hereditary component of risk, the following definitions of degree of relatedness are used:
 - 1st-degree relative: a parent, sibling, or child
 - 2nd-degree relative: a grandparent, uncle, or aunt
 - 3rd-degree relative: a great-grandparent or cousin

Colorectal Cancer

Summary

Most CRC arises from adenomatous polyps, which grow relatively slowly; polyps and colorectal tumors can be detected with varying degrees of sensitivity by any one of several screening techniques, including gFOBT, FIT and endoscopic visualization and biopsy (flexible sigmoidoscopy and colonoscopy). The incidence of CRC increases with age. **The USPSTF and the VA/DoD recommend that persons at average risk be screened for CRC starting at age 50.** In persons at above-average risk, screening should start at an earlier age. The choice of screening procedure (see **Table I**) depends on patient preferences and availability of procedures at particular facilities.

Patients who are HIV-infected may be at slightly increased risk of CRC compared with patients who are HIV-uninfected. However, studies have failed to find an increased risk of CRC in patients with HIV who are on combination antiretroviral therapy.

Epidemiology/Pathogenesis

- Most colon cancers develop from adenomatous polyps; polyps >1 cm in size carry a higher risk than smaller polyps for development of CRC.
- Prevalence of adenomatous polyps increases with age.
- Average lifetime risk of developing colon cancer in the United States is 6%.
- The following confer a higher-than-average risk of developing CRC:
 - History of CRC in a 1st degree relative
 - Family history of large polyps before age 60
 - Ulcerative colitis or Crohn's disease
 - Polyps >1 cm in size
- Patients with specific genetic predisposition to CRC such as familial adenomatous polyposis (FAP) or hereditary nonpolyposis colon cancer (HNPCC) are at extremely high risk of developing CRC.

Screening Methods

- **FIT:** Identifies intact human hemoglobin in stool. These tests are performed at home and do not require dietary modifications and necessitate fewer stool samples than gFOBT. The VA has transitioned from gFOBT to FIT with the exception of some VA emergency rooms.
- **gFOBT:** Detection of blood in a stool specimen by smearing a stool specimen onto absorbent paper impregnated with guaiac, followed by application of hydrogen peroxide; any blood present in the specimen will catalyze the oxidation of guaiac by peroxide, producing a rapid color

reaction. gFOBT can detect blood loss from any point in the GI tract. Can be performed at home using commercial test cards. High-sensitivity FOBT (Hemoccult II or SENZA) is recommended. Dietary modifications (e.g., no red meat, no vitamins) prior to FOBT may not be necessary.

- **CT colonography:** The colon is inflated via a small tube placed into the rectum and imaging is performed.
- **Flexible sigmoidoscopy:** Examination of the colon from the rectum to the splenic flexure, a region in which the majority of malignant lesions arise, with a 60 cm flexible fiberoptic endoscope with biopsy capability.
- **Colonoscopy:** Examination of the entire colon with a 100-160 cm flexible fiberoptic endoscope with biopsy capability.
- Efficacy of screening methods is shown in **Table I**.

Recommendations for CRC Screening

- 80% of CRCs occur in people at average risk.
- Multiple recommended screening methods for average-risk patients. See **Table I**.
- Screening recommendations for higher-risk patients are shown in **Table 2**.
- Screening recommendations for patients at very high risk (individuals with, or relatives of patients with, familial colon cancer syndromes such as FAP or HNPCC) are beyond the scope of this chapter; consultation with GI or Oncology is recommended.
- DRE + FOBT is **not** recommended.
 - Neither sensitive nor specific
 - If performed, a positive result should be followed up with colonoscopy
- Barium enema is no longer recommended by the USPSTF (lower sensitivity than recommended methods).
- Screening of patients aged 76-85 is not routinely recommended.
- Screening of patients >85 years of age is not recommended.

Table I. Recommended Screening Methods for Patients at Average Risk of Developing CRC

Screening Method Recommended by USPSTF	Accuracy and Effective ness	Description/Limitations/ Risks
Home FIT every year	<ul style="list-style-type: none"> • More specific for lower gastrointestinal bleeding than gFOBT 	<ul style="list-style-type: none"> • Patient only submits one specimen • If result is positive, obtain

Screening Method Recommended by USPSTF	Accuracy and Effectiveness	Description/Limitations/Risks
-	<ul style="list-style-type: none"> Improved sensitivity at detecting CRC than gFOBT 	colonoscopy
Flexible sigmoidoscopy every 10 years with FIT every year	<ul style="list-style-type: none"> One study found mortality benefit when compared to flexible sigmoidoscopy alone 	<ul style="list-style-type: none"> Positive FIT result necessitates full colonoscopy, so perform FIT before sigmoidoscopy. Complete or partial bowel prep required before flexible sigmoidoscopy.
Colonoscopy every 10 years	<ul style="list-style-type: none"> ↓ mortality >50% Sensitivity: <ul style="list-style-type: none"> 90% for polyps >1cm 75% for polyps <1cm Colonoscopy has been the reference standard against which FOBT and sigmoidoscopy have been studied 	<ul style="list-style-type: none"> Complete bowel prep required. Colonoscopy can visualize entire colon. Suspicious lesions can be removed for biopsy and as treatment. Greater yield of colonoscopy (most sensitive test for polyps) must be weighed against risks of perforation, bleeding, and conscious sedation, as well as inconvenience of full colonic preparation and conscious sedation. Risk of screening colonoscopy <ul style="list-style-type: none"> Any major complication: 0.3% Perforation: 0.05% Bleeding: 0.15-0.18% Risk of colonoscopy as therapeutic procedure is higher <ul style="list-style-type: none"> Perforation: 0.07-0.72% Bleeding: 0.2-2.7% Risks of procedure are greater in persons >70 years of age, but so are benefits, as proximal lesions are more common in this population.

Screening Method Recommended by USPSTF	Accuracy and Effectiveness	Description/Limitations/Risks
Home gFOBT every year if FIT is not used	<ul style="list-style-type: none"> • ↓ mortality 15-33%, depending on frequency of screening • Leads to more colonoscopies • Annual screening found 49% of cancers; 38% of patients tested required colonoscopy • Screening every 2 years found 39% of cancers; 28% of patients tested required colonoscopy 	<ul style="list-style-type: none"> • Patient submits three 2-window cards, 1 card each from 3 consecutive stools collected at home. • Do not use DRE to collect specimens. • If result is positive in any card window, obtain colonoscopy. • FOBT itself is extremely low risk, but leads to many colonoscopies being performed, with associated risks of bleeding and perforation.
CT colonography every 5 years	<ul style="list-style-type: none"> • Sensitivity: 67-94% for adenomas measuring 10mm or larger in patients who underwent bowel prep • Specificity: unknown 	<ul style="list-style-type: none"> • Limited availability • Radiation exposure • Presence of an adenoma necessitates colonoscopy • Extracolonic findings that ultimately may or may not be of any clinical importance frequently require additional work up.
Flexible sigmoidoscopy every 5 years	<ul style="list-style-type: none"> • ↓ mortality 59% for cancers within reach of sigmoidoscope • Sensitivity: 70-80% • Specificity difficult to define 	<ul style="list-style-type: none"> • Complete or partial bowel prep required. • Misses lesions proximal to the splenic flexure. • Proximal lesions more common in women than men. • Estimated to find 80% of patients with abnormal findings, as distal abnormalities will prompt examination of entire colon with colonoscopy. • Presence of an adenoma generally necessitates full colonoscopy. • Complication rate: <ul style="list-style-type: none"> • Perforation: <0.01% • Bleeding: 2.5-5.5%

Table 2. Screening Recommendations for Patients at Increased Risk of CRC*

Risk Factors	Screening Recommendations
1st degree relative with CRC or adenomatous polyp (AP) diagnosed ≥ 60 years of age OR Two 2nd degree relatives with CRC or AP at any age	Screen as for patient at average risk, but start at age 40. See Table 1.
1st degree relative with CRC or AP diagnosed < 60 years of age OR Two 1st degree relatives with CRC or AP diagnosed at any age	Screening colonoscopy every 5 years, starting at age 40, or 10 years before age at which relative was diagnosed, whichever comes first.
2nd or 3rd degree relative(s) with CRC	Screen as for patient at average risk. See Table 1.
Inflammatory bowel disease (UC or CD)	Colonoscopy every 1-2 years with biopsies for dysplasia. Younger age at diagnosis of CD seems to increase risk, as does distal (colon) vs. proximal (ileum) disease.
Personal history of CRC	<p>Patients with CRC should undergo high-quality perioperative colonoscopy to detect synchronous lesions. Colonoscopy should be performed 1 year after the resection (or 1 year following the colonoscopy that confirmed absence of synchronous disease). If the examination performed at 1 year is normal, then the next examination should be performed in 3 years. If that colonoscopy is normal, then the interval to the subsequent examination should be 5 years. Following the examination at 1 year, the intervals between subsequent examinations may be shortened if there is evidence of hereditary nonpolyposis colorectal cancer (HNCC) or if adenoma findings warrant earlier colonoscopy.</p> <p>If an obstructing tumor prevents high-quality colonoscopy at the time of resection, examination for synchronous tumors can be performed by double contrast barium enema or CT colonography with IV contrast.</p> <p>After low anterior resection of rectal cancer, periodic examination of the rectum may be considered to identify local recurrence. This usually is performed at 3 to 6-month intervals for the first 2 or 3 years.</p>

* **Not including characterized familial colon cancer syndromes** Adapted from Levin et al. See **References**. **Abbreviations:** AP = adenomatous polyp; CD = Crohn's disease; UC = ulcerative colitis

What to Do with a Positive Result

- A positive screening result should be followed by a full colonoscopy, unless contraindicated.
- Patients with negative screening but with symptoms suggestive of CRC or polyps should be offered a full colonoscopy.

Reminders

An example of a typical CPRS reminder for colon cancer screening is shown.

Reminder Resolution: COLORECTAL CANCER SCREEN

Screening for colorectal cancer can be accomplished by one of two options, fecal occult blood detection or colonoscopy. Each method satisfies this screen for different time periods—see below. Testing usually begins at age 50 in the general population. This institution has decided that for general screening, fecal occult blood detection will be the test of first choice.

A. **FECAL OCCULT BLOOD TEST-** satisfies reminder for one year

Most recent FOBT done:

OCCELD1: comment	11/24/1999@12:42 feces
OCCELD2: comment	11/24/1999@12:42 feces
OCCELD3: comment	11/24/1999@12:42 feces

Click here to order Fecal Occult Blood test X 3

Patient's Colorectal Cancer screening is being done by a non VA provider; the most recent FOBT was performed outside this medical center.

B. COLONOSCOPY:

C. REFUSALS:

D. SCREENING NOT MEDICALLY INDICATED DUE TO:

Clear Clinical Maint Visit Info < Back Next > Finish Cancel

<No encounter information entered>

* Indicates a Required Field

Breast Cancer

Summary

Breast cancer is the most common cancer diagnosed among women in the United States. There is no clear evidence that HIV infection increases the risk of breast cancer or alters treatment outcomes; a 2009 meta-analysis suggests that the risk of breast cancer since the availability of effective combination ARV therapy became widespread appears to have increased compared with the earlier years, but that may be attributable to increased survival of patients with HIV infection rather than to a true increased risk of breast cancer. Incidence of breast cancer increases with age, and there is evidence that mammographic screening reduces both incidence and disease-specific mortality. Most cases of breast cancer are detected by mammography. Current USPSTF guidelines recommend

mammogram screening every 2 years for women not at elevated risk of breast cancer. Whereas the benefits of starting screening for women older than 50 are well established, there has been considerable debate about starting screening at age 40. The rate of false-positive screening results in women 40-50 years of age is high, and the benefits of screening need to be weighed against the potential for emotional distress and additional testing caused by false-positive results. In light of a 2009 study that found limited benefit of screening women under 50 years of age, the current USPSTF guidelines state that the benefit of screening for breast cancer in women aged 40-49 is limited. Clinical breast examination (CBE) may be part of screening, depending on patient and provider preference. Breast self-examination (BSE) is no longer routinely recommended by the USPSTF.

Epidemiology

- Lifetime risk of invasive breast cancer in U.S. women is approximately 12.5%; breast cancer is the most common cancer among women in the United States, and the second most common cause of cancer death among women in the United States (after lung cancer).
- Women at increased risk of breast cancer are those with:
 - Family history of breast cancer in a 1st-degree relative
 - Risk higher if multiple 1st-degree relatives with breast cancer
 - Risk higher if affected relatives were <40 years of age when diagnosed
 - Women with a specific mutation conferring risk of breast cancer, such as BRCA1 or BRCA2
 - History of atypical hyperplasia on previous breast biopsy
 - History of first pregnancy after age 30
 - Increased estrogen exposure
 - Early menarche or late menopause
 - Hormone replacement therapy
 - Older age
 - 0.4% annual incidence at age 30-39
 - 1.5% annual incidence at age 40-49
 - 2.8% annual incidence at age 50-59
 - 3.6% annual incidence at age 60-70
- Breast cancer in women <40 years of age appears to be less common but more aggressive. Thus, screening may have less of a protective effect than it does for older women. The increased density of breast tissue in younger women also may reduce the ability of mammography to detect abnormalities.

Screening Methods

- Mammography involves low-dose radiography of the breasts. It should be performed at an accredited, certified facility, with interpretation by an appropriately trained and certified radiologist.
- Clinical breast examination (CBE) and breast self-examination (BSE) are no longer routinely recommended.
- MRI may be useful for women at high risk of breast cancer, who have a need for screening at a younger age, or who have particularly dense breasts. MRI is not routinely recommended for screening women who are not at elevated risk of breast cancer.

Effectiveness of Screening

- Mammography is less reliable (lower sensitivity, specificity, and positive predictive value) in younger women than in older women.
- Sensitivity of mammography is 77-95%.
- Specificity of one-time mammogram is 94-97%.
- Positive predictive value of one-time mammography:
 - 2-22% of women with an abnormal result will require further workup
 - 12-78% of women with an abnormal result will require biopsy
- Mammography reduces breast cancer-specific mortality as much as 31%, depending on the study; meta-analysis finds a reduction in disease-specific mortality of about 15%, including among women <50 years of age.
 - Improvements in the relative risk of death due to breast cancer for women screened with mammography: age 39-49: RR=0.92; age 50-59: RR=0.86; age 60-69: RR=0.67; age 70-74: RR=0.80. Benefits to women older than 75 years of age have not been demonstrated.
- MRI in high-risk women without breast cancer has a sensitivity of 71-100% and a specificity of 81-97%.
- There is no evidence at present that CBE reduces breast cancer-specific mortality.
- Two available studies have indicated no mortality benefit from BSE and an increase in the number of biopsies and additional imaging studies required.

Recommendations for Breast Cancer Screening

- Providers should screen patients for an elevated risk of breast cancer and tailor screening for those at higher risk.
- In women without an elevated risk of breast cancer, conduct screening mammography every 2 years for women 50-74 years of age.

- Providers should discuss screening with women aged 75 and older, taking into account estimated life expectancy and presence of comorbid disease.
- VA facilities with certified mammography sites are listed at <https://vaww1.va.gov/RADIOLOGY/Mammography/VHAMammographySuites.asp>.
- A listing of non-VA certified mammography sites can be accessed at https://vaww1.va.gov/RADIOLOGY/Mammography/Community_FDA_Certified_Sites.asp.
- Further information on mammography is available through the VA Mammography Office at <https://vaww1.va.gov/RADIOLOGY/Mammography.asp>.

Reminders

CPRS reminder definition and resolution options for mammography may differ among VA Medical Centers, depending on local decisions. An example of a typical CPRS reminder for annual mammography is shown.

Reminder Resolution: --MAMMOGRAM 50-69

--Women between the ages of 50-69 should be screened for Breast Cancer with a mammogram every 2 years.

--Order Mammogram

--Mammogram performed elsewhere Location: [dropdown]

Date: * [January] [14] [2002] [.] [..] [..] Results: [text box]

--Patient DECLINES Mammogram Comment: [text box]

--Mammogram NOT applicable due to Bilat Mastectomy

Comment: [text box]

IF YOU HAVE IDENTIFIED THAT THIS PATIENT HAS AN INCORRECT DIAGNOSIS ON FILE. SELECT THE BOX BELOW TO SEND A CONSULT TO PBS FOR CHART CORRECTION.

<---CLICK here to request correction of an incorrect diagnosis!

Clear Clinical Maint Visit Info < Back Next > Finish Cancel

CLINICAL REMINDER ACTIVITY

--MAMMOGRAM 50-69:

Mammogram request order placed.

--Mammogram performed elsewhere

Date: January 14, 2002

Health Factors: DAY INCORRECT DM DX - 14DAY INACTIVATE DAY MAMMOGRAM DONE ELSEWHERE [Historical] DAY MAMMOGRAM N/A BILAT MASTECTOMY DAY MAMMOGRAM REFUSED

Orders: MAMMOGRAM REQUEST, PBS DIAGNOSIS REMOVE

What to do with a Positive Result

- Results should be communicated to the patient as soon as possible. Generally, a lay summary will be sent to the patient by the interpreting radiologist. However, the ordering provider should ensure that results have been communicated to the patient within a reasonable time frame.

- Patients with an abnormal result should be referred to the appropriate service (Women's Health, Gynecology, or General Surgery, depending on the facility) as soon as possible for evaluation and possible biopsy.

Cervical Cancer

Summary

Although there are no randomized controlled trials showing the effectiveness of cervical cancer screening, numerous observational studies have found an association between screening and reductions in the incidence of cervical cancer and disease-specific mortality.

Women with HIV are at elevated risk of cervical dysplasia and cervical cancer. Cervical cancer is highly associated with type 16 and 18 human papillomavirus (HPV) infection (high-risk subtypes). HPV prevalence is higher among women infected with HIV than among HIV-uninfected women, and they have increased persistence of HPV and greater likelihood of infection with high-risk types of HPV. Although the time between diagnosis of carcinoma in situ (CIS) and development of invasive disease is shorter among women infected with HIV who are not on ARV therapy than among HIV-uninfected women, ARV therapy has not been shown consistently to prevent or alter the course of cervical dysplasia. Women with advanced immunosuppression (CD4 count of <200 cells/ μ L) are at higher risk of cervical abnormalities than women with CD4 counts of >200 cells/ μ L. Vaccination against HPV is recommended in females and males infected with HIV ages nine through 26.

The USPSTF and VA/DoD recommend cervical cancer screening using PAP smear or liquid-based cytology in sexually active women with a cervix. In sexually active women, screening should be started at age 21. For women with HIV, most authorities recommend more frequent screening than for HIV-uninfected women.

Population: Women 21 to 65 (PAP smear) or 30-65 (in combo with HPV testing) Recommendation: The USPSTF recommends screening for cervical cancer in women age 21 to 65 years with cytology (PAP smear) every 3 years or, for women age 30 to 65 years who want to lengthen the screening interval, screening with a combination of cytology and human papillomavirus (HPV) testing every 5 years. See the Clinical Considerations for discussion of cytology method, HPV testing, and screening interval.

Epidemiology/Pathogenesis

- Cervical cancer is associated with genital HPV infection; cancer is preceded by identifiable neoplastic changes (cervical intraepithelial neoplasia, or CIN) in the transformation zone of the cervix. Localized cervical cancer is highly curable (5-year survival of 92%), whereas disseminated dis-

ease is not (5-year survival of 13%). Women with HIV progress from CIS to invasive disease faster than HIV-uninfected women. Cervical cancer is an AIDS-defining condition.

- Women at increased risk of cervical cancer include those with:
 - Immunosuppression (including HIV infection)
 - Tobacco use (smoking)
 - Increased risk of HPV infection, such as:
 - Earlier onset of sexual intercourse
 - Multiple sexual partners
 - Sexual partners who have had multiple sexual partners

Screening Methods

- PAP smear: Cervical epithelial cells, collected by brush and spatula, are either smeared directly on a slide and fixed, or suspended in a liquid fixative and spun onto a slide. Liquid-based cytology is preferred, if available, owing to its higher sensitivity. The smear should be examined by an experienced cytopathologist.
- Cervical detection of HPV has higher sensitivity but lower specificity than traditional PAP smear for cervical cancer. The 2003 USPSTF recommendations do not propose HPV DNA testing as a screening method in women infected with HIV. However, recent data suggest that in women with CD4 cell counts of >500 cells/ μL , the combination of a normal PAP smear and the absence of oncogenic HPV is associated with a low risk of cervical dysplasia in the subsequent three years.

Effectiveness of Screening and Screening Interval

- Sensitivity of a single PAP smear for high-grade CIN is 60-80%; specificity is approximately 98%.
- Effectiveness of cervical cancer screening on incidence and mortality of cervical cancer has not been studied prospectively. Nevertheless, data from good-quality case-control and ecological studies show a strong association between screening and reductions in cervical cancer incidence and disease-specific mortality.

Screening Recommendations

Patients <30 years

- Regardless of how HIV was acquired (i.e. perinatal, sexual activity, etc.), screening should begin within one year of first sexual encounter but no later than 21 years.

- Patients 21-29 should be screened at diagnosis of HIV. If PAP is normal, repeat PAP in 6-12 months. Screening interval may be extended to every three years after three consecutive normal PAP tests. Patients with CD4 count <200 cells/uL should be screened every six months.
- HPV co-testing is not recommended in this age group.

Patients >30 years

- Screen at diagnosis of HIV. Screening with PAP testing only or PAP testing with HPV co-testing is acceptable.
- If PAP is normal (no HPV co-testing), repeat PAP in 6-12 months. Screening interval may be extended to every three years after three consecutive normal PAP tests.
- If PAP normal and HPV negative, patient may be rescreened in three years.
- If PAP normal and HPV positive, PAP and HPV co-testing should be repeated in one year. Colposcopy is recommended if the follow up PAP is abnormal or HPV co-testing is positive.
- Because of the increased risk of vaginal cancer associated with HIV infection, women infected with HIV with a history of high-grade CIN or invasive cervical cancer should be screened with regular vaginal cuff PAP smear following hysterectomy.

Reminders

Because the frequency of recommended screening for cervical cancer differs between women who are HIV-infected and HIV-uninfected, the standard CPRS reminder for cervical cancer screening generally is not applicable to the former. HIV providers should work with the local Information Resource Management Service to construct HIV-specific reminders for cervical cancer screening.

What to do with a Positive Result

- Most experts recommend more aggressive management of women who are HIV-infected than women who are HIV-uninfected, while some recommend the same management regardless of HIV serostatus.
- Women who are HIV-infected with CIN generally should be treated according to the latest ASCCP guidelines.

Prostate Cancer

Summary

In contrast to screening for colorectal, breast, and cervical cancer, there is controversy over whether to screen men for prostate cancer. The VA/DoD does not

recommend routine screening, whereas the USPSTF recommends against routine screening.

The American Cancer Society (ACS) recommends that men have a chance to make an informed decision with their health care provider about whether to be screened for prostate cancer. The decision should be made after getting information about the uncertainties, risks, and potential benefits of prostate cancer screening. Men should not be screened unless they have received this information. The discussion about screening should take place at:

- **Age 50 for men who are at average risk** of prostate cancer and are expected to live at least ten more years.
- **Age 45 for men at high risk** of developing prostate cancer. This includes African Americans and men who have a first-degree relative (father, brother, or son) diagnosed with prostate cancer at an early age (younger than age 65).
- **Age 40 for men at even higher risk** (those with more than one first-degree relative who had prostate cancer at an early age).

After this discussion, men who want to be screened should be tested with the prostate-specific antigen (PSA) blood test. The digital rectal exam (DRE) may also be done as part of screening.

Following discussion about the potential risks, benefits, and uncertainties of screening. Although screening is effective at detecting prostate cancer in its early stages, it is not clear that screening reduces disease-associated or overall mortality. Likewise, the effect of treating prostate cancer in its early stages on overall mortality is not clear, and treatment, whether by prostatectomy or radiation, carries a substantial risk of side effects such as urinary incontinence and sexual dysfunction. See below.

The rate of prostate cancer increases over time in men who are HIV-infected, as it does in men who are HIV-uninfected. When corrected for age, men who are HIV-infected seem to be at lower risk of prostate cancer than men who are HIV-uninfected, for reasons that are unknown.

Epidemiology

- Lifetime risk of developing prostate cancer is 16% among men in the United States.
- 10-year risk of developing prostate cancer increases with age, from 0.17% at age 40 to 6.46% at age 60.
- Lifetime risk of death caused by prostate cancer is 2.8% among men in the United States.
- Most deaths resulting from prostate cancer occur at age >65.
- Disease confined to the prostate gland at diagnosis carries a better prognosis than disease extending beyond the gland.

- Incidence of disease and mortality are greater among African American men than among white men in the United States, and among men with a 1st degree relative with prostate cancer.

Screening Methods

- Screening for prostate cancer includes measurement of serum prostate specific antigen (PSA) combined with DRE.
- Prognosis is associated with degree of differentiation of tumor cells (Gleason score) on biopsy and whether disease is confined to the gland or is extraprostatic. Higher Gleason scores (indicating less-differentiated cells) and extraprostatic disease confer a worse prognosis.
- Elevated PSA is associated with prostate cancer, and with benign prostate abnormalities such as benign prostatic hyperplasia (BPH), prostatitis, and trauma to the gland.
- The higher the PSA, the higher the likelihood of prostate cancer, and the higher the likelihood that the cancer has spread beyond the prostate gland.
- **PSA \leq 4 ng/mL** is classified as “normal.” Although up to 27% of men with a PSA $<$ 4 ng/mL will have cancer, most of these will have disease confined to the gland.
- **PSA $>$ 4 ng/mL** is classified as “elevated.” Approximately 1 in 3 men with elevated PSA will actually have cancer. For **PSA 4-10 ng/mL**, 1 in 4 men will have cancer. Most of these cancers will be confined to the gland, but the low positive predictive value of the test means that many men will undergo unnecessary biopsy. For **PSA $>$ 10 ng/mL**, up to two-thirds of men will have cancer and more than half of those cancers will be extraprostatic.

Treatment for Early Prostate Cancer: Side Effects and Benefits

- Treatment consists of active surveillance (watchful waiting), prostatectomy, or radiation therapy.
- Risk of persistent (at least 12 months in duration) side effects from radical prostatectomy:
 - Impaired sexual function: 20-70%
 - Urinary incontinence: 15-50%
- Risk of persistent (at least 12 months in duration) side effects from external beam radiation therapy:
 - Impaired sexual function: 20-45%
 - Urinary incontinence: 2-16%
 - Bowel problems: 6-25%

- When compared with watchful waiting, radical prostatectomy following *clinical* detection of moderately to well-differentiated prostate cancer confined to the gland decreases disease-specific mortality. The effect on overall mortality is less clear. Whether this applies to cancer detected by screening is also not clear.

Effectiveness of Screening

- When analyzed properly, the one randomized trial of screening with PSA and DRE versus no screening showed no mortality benefit from screening.
- Additional prospective trials of screening effectiveness are ongoing.

Screening Recommendations

- Patients should be counseled annually regarding the risks and benefits of screening for prostate cancer by PSA and DRE; screening may be performed if desired by the patient.
- Depending on Veterans Integrated Service Network (VISN), facility, and clinician decision making, prostate cancer screening may be offered to patients deemed to be at increased risk.

Reminders

CPRS reminder definition and resolution options for prostate cancer counseling and screening may differ among VA Medical Centers, depending on local decisions. An example of a typical CPRS reminder for annual prostate cancer counseling and screening is shown.

Reminder Resolution: ---PROSTATE COUNSELING

--There is controversy about whether men over the age of 50 should undergo routine testing each year for early detection of prostate cancer.

Patient advised of the risks and benefits of screening for prostate cancer with PSA blood test. (PSA education handout given to patient)
 Level of Understanding: (None selected) [v]
 Comment: []

Patient requests PSA Test. (place lab order for PSA test)
 Patient declines PSA test at this encounter.

Patient received prostate counseling previously at another facility.
 Date: * January [v] 14 [v] 2002 [v] ... Comment: []
 Location: []

Patient declined prostate counseling at this encounter.
 Comment: []

=====

IF YOU HAVE IDENTIFIED THAT THIS PATIENT HAS AN INCORRECT DIAGNOSIS ON FILE. SELECT THE BOX BELOW TO SEND A CONSULT TO PBS FOR CHART CORRECTION.

=====

<---CLICK here to request correction of an incorrect diagnosis!

Clear Clinical Maint Visit Info < Back Next > Finish Cancel

CLINICAL REMINDER ACTIVITY
 ---PROSTATE COUNSELING:
 Patient advised of the risks and benefits of screening for prostate

Patient Educations: PROSTATE COUNSELING-DISCUSSED
 Health Factors: DAY INCORRECT DM DX - 14DAY INACTIVATE, DAY PROSTATE COUNSELING DONE

What to do with a Positive Result

- Refer to urologist for transrectal ultrasound (TRUS) and biopsy for:
 - Elevation in PSA (PSA >4 ng/mL)
 - Prostatic abnormality (asymmetry, nodule, or induration of the gland) on DRE

Anal Cancer: See chapter **Anal Dysplasia**, p. 315.



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KEY POINTS

- All patients with HIV infection should be offered tetanus, diphtheria, and pertussis (Td or Tdap), hepatitis B, pneumococcal (PPSV23 and PCV13), meningococcal, and inactivated influenza vaccination.
- Other vaccines may be indicated for some patients with HIV. See Immunization Schedule on the next page.
- Live virus vaccines should not be administered to patients with HIV, with the possible exception of measles, mumps, and rubella (MMR) and varicella immunizations and only in those patients whose CD4 counts are >200 cells.



BACKGROUND

- Immunization is a cost-effective, low-risk intervention to prevent morbidity and mortality in patients with HIV.
- The current recommendations regarding immunization of adults with HIV infection are available at the CDC website, <https://www.cdc.gov/vaccines/adults/rec-vac/health-conditions/hiv.html>. VA is not responsible for the content of the linked site. The most recent schedule is shown on the next page.
- All individuals with HIV should be offered both pneumococcal vaccines, meningococcal vaccines, hepatitis B vaccination (if not already immune to HBV); and vaccination with the inactivated trivalent influenza vaccine. Hepatitis A is recommended for patients with HIV and additional risk factors (men who have sex with men, patients who are homeless, people who inject drugs, patients with chronic liver disease, travelers to endemic areas, subjects infected with hepatitis B or C); but per current guidelines, it can be considered for all non-immune subjects. The combined hepatitis A/B vaccines are available at the majority of VA facilities. Hence, we recommend administration of the combined hepatitis A/B vaccine to all patients with HIV who are non-immune to hepatitis A and B.
- Other vaccines should be offered based on specific risk factors. See the next page.
- Live virus vaccines generally should not be administered to patients with HIV; however, administration of MMR, varicella, and zoster vaccines may be appropriate for patients who are asymptomatic, CD4 >200.

Veterans with HIV*

Influenza vaccination: 73%
Hepatitis B immunity or vaccination: 88%

*Veterans in the VA HIV Clinical Case Registry in care in 2010 who received the indicated immunizations; should be offered annually during influenza season

Note: Some medications mentioned in this chapter may not be available on the VHA National Formulary (<https://www.pbm.va.gov/NationalFormulary.asp>). Consult VA pharmacists for alternatives.

Immunization Schedule for Adults with HIV Infection

Vaccine ▼	Indication ►	HIV infection, CD4 T-lymphocyte count	
		<200 cells/ μ L	\geq 200 cells/ μ L
Tetanus, diphtheria, pertussis (Td/Tdap)*	Substitute one-time dose of Tdap for Td booster; then boost with Td every 10 years+		
Human papillomavirus* ¹	3 doses for males (4v or 9vHPV) or females 26 through age 45 years+		
Varicella*	Contraindicated	2 doses+	
Zoster	Contraindicated		No recommendation; may be given if >60 years
Measles, mumps, rubella*	Contraindicated		1 or 2 doses+
Influenza (inactivated)*	1 dose trivalent influenza vaccine (TIV) annually \geq 65, Advisory Committee on Immunization Practices (ACIP) does not make a preference over standard dose or high dose influenza vaccine. +		
Pneumococcal (PPSV23 polysaccharide)	1 dose; if PCV13 given, 8-week interval. One-time revaccination recommended after 5 years (or at age >65 years). If <65, administer another dose at age >65 (if >5 years since prior dose) – (for a total of 2 revaccinations max).++		
Pneumococcal (PCV13 conjugate)*	1 dose; if PPSV23 previously given, one-year interval++		
Hepatitis A*	2 doses++		
Hepatitis B*	3 doses; double-dose may be indicated in some patients i.e., CD4 <200. Repeat series with double-dose may be considered on those that failed to achieve an antibody titer (HBsAb) >10 after a completed vaccination series. +		
Meningococcal*	2 doses of ACWY conjugate vaccine 8 weeks apart, redose every 5 years. ++		

Vaccine ▼	Indication ►	HIV infection, CD4 T-lymphocyte count	
		<200 cells/ μ L	\geq 200 cells/ μ L
Yellow Fever		Vaccine generally should not be administered to immunocompromised patients (strong, moderate). If travel to an endemic area cannot be avoided, vaccination can be considered in the following minimally immunocompromised human immunodeficiency virus (HIV)-infected individuals: asymptomatic adult patients with HIV infection with CD4 T-cell lymphocyte count \geq 200 cells/mm ³ (weak, low) ++	

* Covered by the Vaccine Injury Compensation Program

“Patients with HIV infection should receive the HepB vaccine series (strong, moderate), with consideration of high-dose HepB vaccine (40 μ g/dose) for adults (weak, moderate) and adolescents* (weak, low). One to 2 months after completion, patients should be tested for anti-HBs (antibodies to HepB surface antigen; strong, low). If a postvaccination anti-HB concentration of \geq 10 mIU/mL is not attained, a second 3-dose series of HepB vaccine (strong, low; alternative: 1 dose of HepB vaccine after which anti-HBs is tested*), using standard dose (strong, moderate) or high dose (40 μ g*; weak, low) for children and high dose for adolescents* and adults (strong, low), should be administered.” www.idsociety.org

¹ HPV vaccination is recommended for males or females aged 9-45, 2 doses only may be adequate for individuals <15 yr.

+	For all patients in this category who meet the age requirements and who lack evidence of immunity (e.g., lack documentation of vaccination or have no evidence of prior infection)
++	Recommended if some other risk factor is present (e.g., based on medical, occupational, lifestyle, or other indication)

Adapted from the Advisory Committee on Immunization Practices (ACIP) Adult Immunization Schedule. For detailed information on adult immunizations against influenza, pneumococcal disease, hepatitis B, human papillomavirus, varicella, and hepatitis A, see <https://www.cdc.gov/vaccines/schedules/hcp/adult.html>. VA is not responsible for the content of the linked site.

For information on immunizations against tetanus, diphtheria, pertussis, pneumococcal, measles, mumps, rubella, and meningococcal disease, refer to recommendations of the ACIP on the CDC website, <http://www.cdc.gov/vaccines/pubs/ACIP-list.htm>. VA is not responsible for the content of the linked site.



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KEY POINTS

- Polypharmacy is defined as taking five or more medications and the use of inappropriate drug therapy.
- Polypharmacy is more common in patients with HIV compared to members of the general population. For the treatment of HIV alone, patients are often prescribed three or more agents in combination. The adverse effects of highly active antiretroviral therapy (HAART) also increase the risk for comorbidities that require treatment.
- HAART inhibits HIV-1 replication in cells. It is associated with drug interactions with commonly used medications, including acid-suppressing drugs, erectile dysfunction drugs, statins, anticonvulsants, antifungals, and warfarin, among others.
- Today, with advances in HAART, treatment can be as simple as one pill once a day. When Veterans with HIV are diagnosed with HIV early, they can be started on life-saving treatment that ensures they live long, healthy lives.
- Accurate medication histories are a significant part of evaluating for polypharmacy and making improvements to drug regimens. Validated tools exist to aid healthcare providers in evaluating if medication therapies are potentially inappropriate.



BACKGROUND

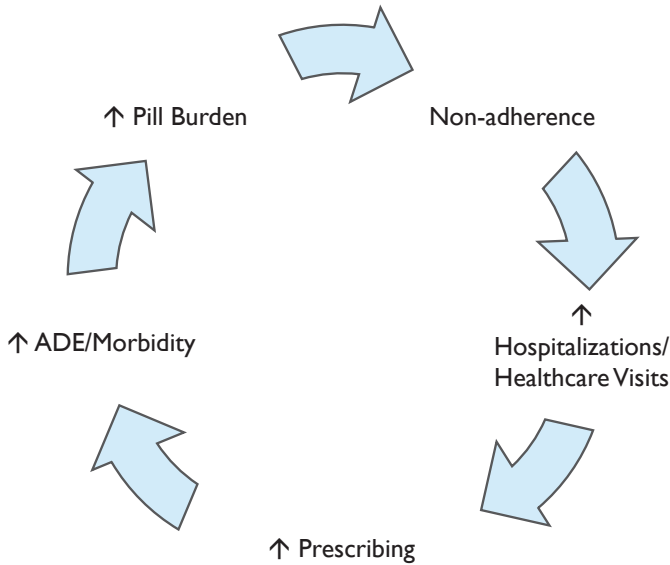
Polypharmacy is increasingly recognized as a significant barrier to the treatment of human immunodeficiency virus (HIV) infection and to the quality of life of patients who are affected. Advancements in the treatment of HIV infection have resulted in longer life expectancy. However, this success has also been countered by other challenges for patients and healthcare providers.

Polypharmacy Defined

Polypharmacy is most commonly defined as taking five or more medications and the use of potentially inappropriate drug therapy. Polypharmacy poses many risks that can be associated with increased morbidity and mortality, as will be discussed further. It has been noted in the medical literature as the strongest predictor for serious adverse drug events (ADE).

Polypharmacy can result in a vicious cycle in which high pill-burden leads to non-adherence, which further leads to increased hospitalizations, increased prescribing, and increased adverse drug events and morbidity. Consequently, it is critical to evaluate the risk factors for polypharmacy, the potential complications, and the various strategies to combat this often-silent threat.

Note: Some medications mentioned in this chapter may not be available on the VHA National Formulary (<https://www.pbm.va.gov/NationalFormulary.asp>). Consult VA pharmacists for alternatives.



Risk Factors for Polypharmacy

For the general population, there are multiple risk factors for polypharmacy, including patient-related characteristics, health-system barriers, and access to care. Patients may have individual-related barriers, including poor health literacy, financial challenges, and social and/or personal stresses that contribute to non-adherence and polypharmacy. Health-system related barriers, such as formulary or insurance restrictions, may also interrupt care or lead to additional challenges. Access to care may also contribute to this problem when patients have difficulty attending follow-up appointments due to transportation issues or personal or professional reasons. These challenges disrupt continuity of care and contribute to polypharmacy.

Prevalence of Polypharmacy in Patients Who are HIV-infected

Polypharmacy is more likely to occur in patients who are HIV-positive compared to members of the general population. For the treatment of HIV, patients are often prescribed three or more agents in combination for therapy. This inherently increases the risk for polypharmacy.

Highly active antiretroviral therapy (HAART) prolongs short-term survival in patients with HIV/AIDS. With the increased life-expectancy with HAART comes an increase of chronic noninfectious comorbid diseases. For example, HAART

has been associated with cardiovascular disease, diabetes, and renal and bone diseases. Therefore, many patients who are HIV-infected are prescribed additional medications, such as acid-suppressing therapies and lipid-lowering medications that can affect the safety and efficacy of HAART.

In addition, because patients with HIV are expected to remain on HAART for the remainder of their lives, compliance and polypharmacy increasingly pose a challenge to the efficacy of therapy and quality of life as this population ages. Studies have found that as patients with HIV age, they are at an increased risk for neurocognitive and substance-use disorders compared to the uninfected population. This may be attributed to poor social support and other factors that impact adherence. Approximately 30% of adverse drug events reported in one study were found to be preventable. Therefore, it is important to recognize these potential complications in all patients, particularly in people with HIV.

Assessment for Inappropriate Therapy in Older Adults

Who are HIV-infected

Validated tools exist to aid healthcare providers in evaluating if medication therapies are potentially inappropriate for older adults. Examples of these tools include the Beers Criteria and Screening Tool of Older Persons' potentially inappropriate Prescriptions (STOPP). In a prospective, randomized trial, investigators identified inappropriate prescribing of medications in 63% and 54% of patients aged 50 or older using the BEERs and STOPP criteria, respectively. After a visit with the pharmacist, 10% of patients had 6 or more medications discontinued. Reasons for discontinuation included, but were not limited to, drug class duplications and drug-drug contraindications.

Implications of Polypharmacy in Patients with HIV

Polypharmacy poses a significant risk in the setting of pharmacokinetic and pharmacodynamic drug interactions, adverse drug events, non-adherence, and economic burden.

Common Drug-Drug Interactions

HAART is associated with many drug interactions with other commonly used medications. The following section is not an all-inclusive review of drug interactions with HAART; however, several potential interactions with common medications are listed. Providers should consult dosing information, and a thorough review of patients' medication lists should be completed to ensure medications are appropriately dose-adjusted and medication contraindications are avoided.

Abbreviations: *RAL= raltegravir; NNRTIs= Non-Nucleoside Reverse Transcriptase Inhibitors; PIs= Protease Inhibitors; ATV= atazanavir; IDV= indinavir; RPV=

rilpivirine; NVP= nevirapine; ETR= etravirine; TPV= tipranavir; EFV= efavirenz; FPV = fosamprenavir

- Acid-suppressive therapy
 - Proton pump inhibitors (PPIs)
 - Integrase inhibitors: increase RAL levels
 - NNRTIs: decrease RPV levels
 - PIs: decrease ATV and IDV levels. TPV decreases Omeprazole AUC.
 - H₂ Receptor Antagonists (H₂RAs)
 - Decrease ATV levels
 - Decrease RPV levels
 - Antacids
 - Decrease RPV, ATV, FPV, TPV levels
 - May bind integrase inhibitors
- PDE 5 inhibitors for erectile dysfunction (sildenafil, vardenafil, tadalafil)
 - concurrent boosted PI or boosted integrase inhibitor single tablet regimens (Genvoya, Stribild) essentially quadruples dose and doubles the half-life of all of the PDE 5 inhibitors; e.g., 25 mg of sildenafil will act like 100 mg and the duration of action increases from four to eight hours
- Statins
 - NNRTIs: EFV may induce statin metabolism
 - Simvastatin and Lovastatin
 - Contraindicated with boosted PI or boosted integrase inhibitor single tablet regimens (Genvoya, Stribild)
 - Atorvastatin and Rosuvastatin
 - Concurrent boosted PI or boosted integrase inhibitor essentially doubles dose; e.g., 10 mg will act like 20 mg
- Antiepileptics
 - CYP450 inducers, such as phenobarbital, phenytoin, or carbamazepine may decrease PI, INSTI and NNRTI levels and coadministration with these antiepileptics is not recommended for several of these ARVs
- Antifungals
 - Fluconazole
 - NNRTIs: increase NVP levels; may increase ETR and RPV levels
 - PIs: increase TPV levels
 - Itraconazole
 - NNRTIs: EFV, ETR, and NVP may decrease itraconazole levels; may increase ETR and NVP levels
 - PIs: may increase PI levels and increase itraconazole levels
 - Posaconazole

- NNRTIs: EFV can decrease posaconazole levels; posaconazole can increase ETR levels
- PIs: increase RTV and ATV levels
- Antihyperglycemics
 - Saxagliptin levels increase with PIs and EVG/c and can cause significant hypoglycemia. Dose adjustment needed.
- Hormonal therapy
 - Hormonal contraceptive: Interactions with several PIs and NNRTIs can cause alterations in serum levels of either the contraceptive or ARV
 - Corticosteroid levels increase with PIs and EVG/c and risk of adrenal insufficiency increases
- Warfarin
 - NNRTIs: INR should be monitored closely when stopping or starting NNRTIs; may either increase or decrease warfarin levels
 - PIs: INR should be monitored closely when stopping or starting PIs; may either increase or decrease warfarin levels
- Other anticoagulants/antiplatelet drugs
 - PIs or EVG/c should not be coadministered with apixaban/betrixaban/edoxaban/rivaroxaban/ticagrelor/vorapaxar
 - COBI should not be coadministered with dabigatran
- Antidepressants/Antipsychotics/Anxiolytics
 - With PIs, dose titration of SSRIs, quetiapine, TCAs, bupropion and other antipsychotics is needed as PIs affect levels of these mood meds
 - With PIs and EVG/c, pimozide/lurasidone are contraindicated
 - EFV is contraindicated with pimozide
- Cardiac medications
 - PIs increase levels of all antiarrhythmics and coadministration is not recommended
 - PIs and EVG/c increase levels of ranolazine/ivabradine and are contraindicated with these
- Narcotic Replacement Therapy
 - Methadone and EFV should not be coadministered; EFV reduces methadone concentrations and may cause withdrawal symptoms
 - Buprenorphine and ATV should not be coadministered
- QTc-prolonging Drugs
 - Avoid EFV and RPV if taking other QTc-prolonging meds as they can cause torsades-de-pointes
- Anti-mycobacterial Meds

- TAF should not be used with any rifamycin
- RAL dose should be increased to 800 mg twice a day if Rifampin is used
- DTG with Rifampin is safe only if no selected INSTI mutations present
- PI-regimens are safer with rifabutin than rifampin
- Rifampin is contraindicated with NNRTIs except EFV (EFV dose needs to be increased and monitored) and with RAL once-daily dose
- Rifabutin should not be coadministered with EVG/c

Regimens that Should Be Taken with Food

- ATV/r- or ATV/c-based regimens
- DRV/r- or DRV/c-based regimens
- EVG/c/TAF/FTC
- EVG/c/TDF/FTC
- RPV-based regimens

Regimens that Should Be Taken on an Empty Stomach

- EFV-based regimens

Adverse Drug Effects

Studies have shown that polypharmacy may be independently related to falls and fall-related injuries. As the HIV population ages, patients often become more frail and have a heightened sensitivity to medication-related interactions and adverse effects. Huang and colleagues noted that the prescription of 4 or more medications was associated with a higher risk of falls in an adult diabetes population. Deandrea and colleagues performed a meta-analysis to assess risk for falls in older adults. The authors found a 5% increase in fall risk associated with each additional medication in older adults of the general population. Another study found that with each additional medication patients were taking, the mean number of ADE per patient increased by 10%. In this study, 35% of healthcare visits to either an urgent care clinic, emergency department, or other healthcare facility were attributed to avoidable adverse events.

HAART can be associated with multiple comorbidities, as previously mentioned. These comorbid disease states often warrant the initiation of one or more drug therapies. For example, one study found that 81% of patients who sustained a fracture also experienced a fall as the source of the fracture. Given the association between HAART therapy and decreased bone mineral density, especially with TDF, it is particularly important to address this complication of HIV. However, as more therapies are added to a patient's drug regimen, the risk for polypharmacy increases. Therefore, proper medication therapy management is crucial

in composing an individualized treatment regimen for patients that assesses the risks versus benefit for each therapy.

Non-adherence

Non-adherence to therapy is an important factor to consider. As the number of medications and the frequency of medication administration increases, this can lead to a significant set-back in compliance to therapy in the outpatient setting. If HAART and opportunistic infection prophylaxis are not consistently and appropriately administered by patients, the implications of this could have a significant effect on morbidity and mortality in this patient population and could potentially lead to antimicrobial resistance to therapy. Therefore, it is imperative for healthcare providers to collaborate with patients to tailor a drug regimen that is feasible for compliance and adequate to maintain quality of life.

Economic Burden

Finally, polypharmacy can produce a substantial economic burden on healthcare systems, society, and individual patients. High drug costs can be a barrier to treatment for patients, and increased prescribing from multiple providers can contribute to this. Costs due to increasing healthcare visits should also be considered. For example, when patients experience adverse events or experience outcomes of non-adherence to therapy, higher costs are associated with increased primary care or urgent care clinic appointments, emergency department visits, and hospitalizations. Using data from the National Electronic Injury Surveillance System Cooperative Adverse Drug Event Surveillance project, one study found that nearly half of the hospitalizations for ADE were among adults 80 years or older, and there were nearly 100,000 emergency hospitalizations for ADE in U.S. adults aged 65 years or older from 2007 to 2009. Increased visits and stays in healthcare facilities produces higher risk for healthcare-associated infections, as well. Additionally, there are unaccounted costs for patients who are unable to attend work or other daily duties. Furthermore, this may lead to interruptions in therapy when the need for healthcare visits occurs.

Management and Prevention of Polypharmacy in Patients Who are HIV-Infected

Various strategies can be employed to combat polypharmacy. Accurate medication histories are a significant part of evaluating for polypharmacy and making improvements to drug regimens. Without an accurate medication history, providers may not be aware of medication duplications, inappropriate dosing of medications, drug-drug interactions, medications prescribed without any evident indications, and potentially harmful ADEs that may deem a drug inappropriate for certain patients. It is also beneficial to perform medication education for patients. Patients are better equipped to take an active role in their healthcare when they

understand their disease states, the indications for their medications, how to administer medications appropriately, and how to identify medication-related adverse effects that should be reported to providers. Finally, adherence tools can be successful in targeting “pill burden.” Examples of adherence tools can include pill boxes, medication charts or journals, and medication-related technology, including applications on a cellular device. These simple tools may have a significant impact in improving patient care and empowering patients to take ownership of their health.



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Important or High-Risk Populations

KEY POINTS

- Homelessness disproportionately affects U.S. military Veterans.
- Veterans comprise 7.9% of the U.S. population, but make up 11% of the American homeless population.
- In January of 2017 it was estimated that there were at least 40,056 homeless Veterans in the United States.
- Over the course of a year, almost 140,000 Veterans use shelter services.



BACKGROUND

In a sample of 164,933 Iraq/Afghanistan War Veterans, 4% had a history of homelessness. Those who were homeless were more likely to be suicidal (17% vs. 3%) and those who were suicidal were much more likely to be homeless (21% vs. 4%). Those Iraq/Afghanistan War Veterans with the Polytrauma Clinical Triad (post-traumatic stress disorder, traumatic brain injury, and chronic pain) and a chronic medical condition were more likely to be homeless.

Risk Factors for Homelessness among Veterans

- Unmarried Veterans are twice as likely to become homeless.
- African American Veterans or those with an annual income of <\$25,000 are 1.5 times more likely to become homeless.
- A history of incarceration is associated with mental illness and substance abuse.
- Transgender status such as homeless transgender Veterans are more likely to have HIV infection.
- Post-traumatic stress disorder is a factor in homelessness.
- A history of military sexual trauma doubles the risk of homelessness.
- A dishonorable or other-than-honorable discharge is associated with homelessness.
- A lower military pay grade can affect homeless status.
- Veterans with <50% service-connected disability are at risk.
- Substance use disorder doubles the risk of homelessness among Veterans.
 - Substance abuse decreases opportunities for obtaining housing or employment, increases interpersonal conflict, increases the risk for HIV infection and other health problems, and increases exposure to criminality, either through arrest or victimization.

Note: Some medications mentioned in this chapter may not be available on the VHA National Formulary (<https://www.pbm.va.gov/NationalFormulary.asp>). Consult VA pharmacists for alternatives.

In 2013, the Secretaries of Departments of Housing and Urban Development and Veterans Affairs (Shaun Donovan and Eric Shinseki) issued a joint statement on the problem of Veteran homelessness.

The reasons for [high rates of Veteran homelessness] are not all related to military service; however, combat, wartime trauma, and posttraumatic stress disorder sometimes contribute to a downward spiral of depression, substance abuse, broken relationships, unemployment, and isolation—which may lead to homelessness.

Specific Problems Higher in Homeless Veterans

Veterans have higher rates of comorbidities than the general population so their health problems are amplified by homelessness.

Suicide: Suicide rates per 100,000 population (Hoffberg et al., 2015)

- U.S. National rate: 12.6
- Rate among U.S. Veterans: 39.0
- Rate among homeless Veterans: 81.0

Mortality: Homeless Veterans have a 32.3% increase in all-cause mortality compared to non-homeless Veterans, after controlling for age, race, gender, severe mental illness, substance abuse, and medical comorbidities. (LePage et al., 2014)

Poor diabetes control: 21.4%

Fluid/electrolyte disorders: 20.4%

Liver disease: 18.8%

Psychosis: 39.7%

Depression: 42.3%

Substance abuse: 46.7% (Axon et al., 2016)

Food Insecurity

- A common problem among the homeless is food insecurity.
- Food insecurity is a risk factor for several worse health outcomes, including:
 - Poor glycemic control in diabetes mellitus;
 - Higher viral load and lower CD4 counts in patients with HIV infection;
 - Higher blood pressure; and
 - Worse depressive symptoms.
- Food insecurity causes a reliance on inexpensive foods that are not optimal for glycemic control, creates competing demands between food

and healthcare expenditures, and may result in decreased adherence and efficacy of medications that require concurrent food consumption to optimize oral absorption.

- Malnutrition is associated with:
 - decreased functional status;
 - loss of bone and muscle mass;
 - immune deficiency;
 - anemia;
 - cognitive dysfunction;
 - delayed wound healing and recovery from surgery; and
 - increased hospital and readmission rates and mortality.

Compared to Homeless Non-Veterans, Homeless Veterans are:

- Older, more likely to be male, and better educated;
- More likely to separated, widowed, or divorced;
- Less likely to ever be married;
- More likely to abuse alcohol, illicit drugs, and tobacco;
- More likely to suffer frostbite or trench foot, pulmonary disease, hypertension, diabetes, and tuberculosis; and
- More likely to have HIV infection and other sexually transmitted infections.

The Effect of Homelessness on Healthcare Services Utilization

- Veterans who are homeless have greater unmet health needs than those with stable housing: medications; dental and eye care; medical, surgical, and psychiatric care.
- The homeless face multiple barriers to obtaining health care, including limited transportation, decreased availability and fragmentation of health-care services, difficulty scheduling and keeping appointments, lack of trust, social isolation, and competing sustenance needs.
- Homeless Veterans over-utilize emergency services (6.6 times more likely to be among the most frequent emergency department users).
- Homeless users of VA emergency care are more likely to be younger, have hepatic disease, have HIV infection or AIDS, or have a psychiatric disorder.
- Homeless Veterans underutilize primary care and have longer stays at higher levels of acuity during hospitalizations.

- In one study, the average length of a hospitalization for an individual who is homeless was 36% longer than for a non-homeless individual's hospitalization for the same problem.
- In a study comparing homeless older adults who obtained housing versus those that did not, the former had a lower rate of acute care visits (2.5 visits a year) versus 5.3 visits a year for those that remained homeless.

The Epidemiology of HIV, Hepatitis C, and Hepatitis B Infection in Homeless Veterans

Due to the overlapping risk factors of psychiatric disorders and substance abuse, homeless Veterans are at high risk for blood-borne viral infections, with rates of infection 2.5-4.5 times that of non-homeless Veterans. See **Tables 1 and 2**.

Table 1. Prevalence of Blood-borne Viral Infections in Homeless vs. Non-Homeless Veterans in 2015¹

Viral Infection	Homeless Veterans Tested, %	Homeless Veterans Infected, %	Non-Homeless Veterans Infected, %	US Population Infected, %	Ratio Homeless/ Non-Homeless Veterans
HIV	63.8	1.52	0.44	0.39 ²	3.5
HCV	78.1	12.1	2.7	1.0 ³	4.5
HBV	52.8	0.99	0.40	0.27 ³	2.5

¹Based on 242,740 homeless Veterans in VA care in 2015

²Centers for Disease Control and Prevention. Statistics overview: HIV prevalence estimates. Available at <http://www.cdc.gov/hiv/statistics/overview/>.

³From National Health and Nutrition Examination Survey (NHANES)

Table 2. Prevalence of HIV, Hepatitis C, Hepatitis B, HIV/Hepatitis C Co-infection in male and females, Homeless vs. Non-Homeless Veterans, % (2015)

	HIV		HCV		HBV		HIV/HCV coinfection	
	Home Less	Non-homeless	Homeless	Non-homeless	Homeless	Non-homeless	Homeless	Non-homeless
Male	1.64	0.46	13.1	2.9	1.03	0.40	0.5	0.08
Female	0.58	0.19	3.9	1.3	0.62	0.36	0.09	0.02

Ratio Male/ Female	2.8	2.4	3.4	2.2	1.7	1.1	5.6	4.0
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Based on VA data from 2015, testing for blood borne viruses in homeless Veterans was inadequate; only 52.8 and 63.8% of homeless Veterans were tested for HBV and HIV, respectively. Hepatitis C testing rates were higher (78.1%). HCV was the most prevalent of the three-blood borne viral infections and it was 4.5-times more common in homeless versus non-homeless Veterans and 12-times more common than in the U.S. population. HIV and HBV infections were 3.5- and 2.5-times more common in homeless Veterans, versus the non-homeless. In homeless Veterans, HIV, HCV, HBV, and HIV/HCV coinfections infections were 2.8-, 3.4-, 1.7-, and 5.6-times more common in males compared to females, respectively. Nevertheless, homeless females were much more likely than their non-homeless counterparts to have blood borne viral infections. The HIV/HCV coinfection rate was 6.3-times higher in homeless male Veterans compared to non-homeless male Veterans. These statistics highlight the greater problem of blood borne viral infections in the homeless Veteran population.

About 3.4% of the overall U.S. homeless population are HIV-infected, compared with 0.4% in the general population. However, prevalence rates in homeless men who have sex with men and injection drug users are much higher, at 30% and 8%, respectively. Homeless or marginally housed patients with HIV suffer delays in HIV diagnosis and entry into care as well as lower rates of continuity of care. In a 2007 multi-site study in the USA, a larger proportion of homeless patients with HIV had CD4 cell counts below 200 cells/mcL (43 vs. 32%) and detectable HIV viral loads (65 vs. 51%) compared to non-homeless patients with HIV.

Adherence to HIV treatment is lower in those with underlying depression and/or substance abuse.

In a study looking at the effect of substance abuse for homeless patients with HIV and a comparator group, the level of non-adherence to antiretroviral (ARV) therapy depended on the abused drug. The respective adjusted odds ratio for non-adherence to ARV therapy for marijuana, crack cocaine, and alcohol abuse were 2.08, 2.09, and 2.98, respectively.

Homeless patients with AIDS have higher mortality rates compared to the non-homeless. In a study of 6558 patients with AIDS conducted in San Francisco, 67% of the homeless group survived five years versus 81% of those with housing ($p < 0.0001$). Conversely, homeless patients with AIDS who obtained supportive housing had a decreased risk of death versus those who did not (Relative Hazard 0.20). Contributing factors to the increased mortality in the homeless patients with AIDS included drug use, mental illness, inadequate health care use, and medication non-adherence.

In one trial of immediate housing and case management conducted in non-Veteran homeless patients with HIV, a greater proportion of patients in the intervention arm attained a primary endpoint of CD4 count ≥ 200 cells; how-

ever, survival and HIV viral load levels were not significantly different in the two groups.

The Problem of Tuberculosis in the Homeless

TB incidence in the homeless in the United States is 46-times the general population.

- The high incidence of TB in the homeless is due to the overcrowding of high-risk individuals, poor ventilation.
- Alcohol and illicit drug use, incarceration, and underlying psychiatric illness contribute to difficulties in the diagnosis and treatment of TB in the homeless.
- The transient nature of the homeless population makes contact identification and tracking difficult, and results in delays in diagnosis and treatment.
- Poor compliance with TB treatment regimens leads to increased morbidity and mortality compared with the general population.
- TB prevalence in patients with HIV is doubled for those who stay in shelters versus those who do not.

TB Control Strategies used to improve detection and treatment in the homeless include:

- Screening by interferon (IFN)-gamma release assays or chest radiography instead of PPD skin testing;
- CDC guidelines recommend IFN-gamma release assay as preferred method given improved test characteristics and ease of testing. See <https://academic.oup.com/cid/article/64/2/111/2811357>;
- Incentives to promote screening and treatment;
- Directly Observed Therapy; and
- Simplified treatment regimens, e.g., 12-dose regimen of isoniazid/rifampentine for latent TB.

Other Infectious Disease Problems in the Homeless

- Scabies and body louse infestations are more common in the homeless; lice can transmit *Bartonella quintana*, which can cause trench fever, peliosis hepatis, endocarditis, and bacillary angiomatosis.
- Community-acquired pneumonia and influenza are common in the homeless populations due to overcrowding, smoking, alcohol use, and chronic lung disease; vaccination against pneumococcal pneumonia and influenza are underutilized in the homeless.
- Homelessness is associated with higher rates of tinea pedis, impetigo, and folliculitis.

The Imperative to Control HIV Infection among the Homeless

Survival sex (exchanging sex for money or drugs) may increase HIV transmission risk and may be more common in the homeless. To address the high risk of HIV transmission from the homeless to their sexual and drug-abusing partners, a number of interventions have been proposed:

- Housing First as a priority;
- Outreach programs for the homeless which include HIV testing and linkage to care;
- Antiretroviral adherence support;
- Harm Reduction with respect to intravenous drug use (needle exchange programs, opioid substitution therapy, supervised injection sites); and
- Directly-observed antiretroviral treatment delivered free-of-charge.



EVALUATION

Screening for HIV Infection in Homeless Veterans

Outreach events sponsored by VA have been used to engage homeless Veterans in care and to provide a venue for rapid testing for HIV infection. HIV screening is also a component of entry into VA care and the clinical reminders administered annually to outpatients as part of their primary care encounters.

Screening for Homelessness among Veterans and VA Resources for the Homeless

Because patients may be embarrassed to report housing instability to their healthcare providers, VA administers the Homelessness Screening Clinical Reminder (HSCR) annually to outpatients as part of their primary care encounters. The purpose of the HSCR is to link Veterans to services that facilitate housing stability. In 2014, among the almost 4 million Veterans who were screened by the HSCR, 0.8% screened positive for homelessness and 0.7% screened positive for being at risk for homelessness.

The U.S. Department of Housing and Urban Development-Veterans Affairs Supportive Housing (HUD-VASH) program combines Housing Choice Voucher (HCV) rental assistance for homeless Veterans with case management and VA clinical services. Since 2008, HUD-VASH has awarded over 85,000 vouchers based on geographic need and public housing agency (PHA) administrative performance. After determining areas with the highest number of homeless Veterans, VA Central Office identifies VA facilities in those areas. HUD selects PHAs near the identified VA facilities, and invites PHAs to apply for vouchers. However, the number of homeless Veterans often outnumbers the available vouchers.

In 2012, VA made Housing First the basis for the HUD-VASH program. The Housing First concept is based on the premise that long-term housing provides the requisite stability to obtain other beneficial services such as mental health and medical care, case management, or employment.

Several VA hospitals have recently implemented homeless-focused medical homes, Homeless Patient–Aligned Care Teams (H-PACTs), that incorporate primary and mental healthcare, substance abuse treatment, and case management into an integrated unit. The H-PACT model was launched in 2011 as part of the Ending Homelessness Among Veterans initiative. In 2017, there were over 60 VA facilities utilizing H-PACTs, serving about 19,000 patients. There are four core elements of an H-PACT that distinguish it from traditional primary care: (1) facile access to primary care with flexible scheduling and clinical outreach to patients who are homeless in community locations; (2) integrated services or co-located mental health/ primary care services and sustenance assistance (e.g., food/food vouchers, hygiene facilities, clothing, transportation resources); (3) intensive healthcare management integrated with community agencies with an emphasis on continuity of care; and (4) staff training on homeless care issues. In one study, patients who are homeless enrolled in an H-PACT for at least 1 year averaged 3.4 clinic visits with their primary care provider (PCP) and averaged 1.5 visits in a specialty clinic, and 82% were receiving mental health and substance abuse care. By comparison, patients in general VA primary care clinics averaged 1.8 PCP visits per year.

In a survey of VA H-PACTs conducted in 2015, 82% of sites provided hygiene support (showers, hygiene kits, and laundry assistance); 76% transportation assistance; 55% had a clothes pantry on-site; 42% provided food assistance (e.g., meals, food pantry access, food stamp applications), 39% had peer mentors to facilitate care navigation; 30% had vocational programs; 27% processed benefits and disability claims; and 21% provided legal aid.

R_x MANAGEMENT

Healthcare for Homeless Veterans (HCHV) Program

- Conducts outreach to those not receiving VA services and engages them in treatment programs.
- Provides per diem payments to non-VA facilities to provide housing, outreach services, case management, rehabilitation, and healthcare to Veterans who are homeless.
- Sponsors Contract Residential Treatment programs, which place Veterans with mental health diagnoses into supportive housing.
- Provides access to vocational specialists and community employment opportunities.

Transitional Living Facilities

VA facilities also provide various transitional living facilities for short-term (3-6 months) housing. These facilities require that the Veteran participate in appropriate therapeutic groups or treatments.

Veterans Justice Outreach

This service advocates for the Veteran within the legal system, to address treatment as an alternative to incarceration.

Compensated Work Therapy

Provides a therapeutic multi-step program for the unemployed Veteran with goal to place in competitive employment.

Support Services to Veterans and Families (SSVF)

Provides funds to assist with securing a lease or avoiding eviction.

Housing Opportunities for Patients with AIDS (HOPWA)

The HUD HOPWA program enables patients with HIV to obtain housing in the private market by providing rent subsidies. The assisted households are responsible for paying 30% of their monthly income for rent and utilities and the program pays the remainder. Ninety percent of households receiving HOPWA assistance have very low incomes. In 2015, 11% of the 2,443 new HOPWA housing recipients were Veterans.

National Call Center for Homeless Veterans: 877-424-3838 (877-4AID-VET). Veterans can call to receive information about local Veterans homeless programs.



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Lesbian, Gay, Bi-Sexual, and Transgender (LGBT) Health

KEY POINTS

- It is important to understand the terminology used to define and to describe sexual and gender minorities.
- LGBT people experience barriers to accessing health care.
- Unique primary care needs arise when “safe sex fatigue” occurs.
- A sexual health assessment should be conducted with all Veterans and attention given to LGBT health disparities.
- Rx management and interactions directives are updated on the Pharmacy Benefits Management (PBM) Services website.
- VA offers various LGBT-affirming services to ensure a welcoming environment for LGBT Veterans.
- VA outlines policy, trainings and resources through various online sites listed below.

VA Serves All Who Served. Per VHA Directive 1340 (Provision of Health Care for Veterans who Identify as Lesbian, Gay, or Bisexual), VA provides equitable, respectful, and affirming health care that is clinically appropriate to lesbian, gay, and bisexual (LGB) Veterans. VHA Directive 1341 (Providing Health Care for Transgender and Intersex Veterans) also mandates that VA provide equitable, respectful, and affirming health care that is appropriate for transgender and intersex Veterans.

Sexual Identity & Sexual Orientation

Basic Terminology and Key Concepts

There are distinct differences between sexual orientation, sex, and gender, although these terms are often conflated with one another. See **VHA Directive 1341**, https://www.va.gov/vhapublications/ViewPublication.asp?pub_ID=6431 for updates.

- **Sex:** Classification based on primary and secondary sex characteristics. Often referred to as “sex assigned at birth” based on the newborn’s genital appearance (e.g., male, female, intersex).
- **Gender:** Behavioral, cultural, and psychological traits often associated with a person’s sex. For example, man, woman, or something else (e.g., transgender; androgynous).
- **Gender Identity:** A person’s internal sense of gender; that is, sense of self as a man or woman, transman or transwoman, genderqueer, two-spirit, or something else. Everyone has a gender identity. Gender identity is distinct from sexual orientation.

Note: Some medications mentioned in this chapter may not be available on the VHA National Formulary (<https://www.pbm.va.gov/NationalFormulary.asp>). Consult VA pharmacists for alternatives.

- **Sexual Orientation:** A term referring to a person's emotional and/or sexual attraction to people of the same/or different sex or to both sexes. Everyone has a sexual orientation. However, for many reasons, the identity label an individual uses may differ from their sexual orientation. People often choose to identify themselves as *gay*, *lesbian*, *bisexual*, or *heterosexual/straight*. However, there are many other terms that people use to describe their sexual orientation. *Homosexual* is generally viewed as a pejorative term. It is best to use whatever term the Veteran identifies as fitting their sexual orientation.

Note about Sexual Orientation

Some people engage in sexual behaviors that are not congruent with their identified sexual orientation. For example, **men who have sex with men (MSM)** is a term often found in HIV epidemiological research. This term is used to identify men who engage in same-sex behavior who may or may not label or identify themselves as gay or bisexual. **Thus, it is important to not make assumptions about identity, sexual behavior, and associated risks. Ask Veterans how they identify their sexual orientation to know how to address them appropriately and know which health risks to consider for follow-up assessment. Ask Veterans about their sexual behavior to understand their sexual health history and potential behavioral risks.**

- **Cisgender:** A term used when sex and gender identity are congruent. For example, a Veteran whose sex assigned at birth was female and identifies as a woman. Sometimes also referred to as *cis*.
- **Transgender:** An umbrella term used for people whose gender identity is not congruent with their sex assigned at birth. For example, a Veteran whose sex assigned at birth was male but identifies as a woman. Individuals who do not identify as cisgender are considered gender minorities. Gender minority individuals may identify as transgender or use another term, such as man or woman, gender fluid, gender non-conforming, masculine, feminine, androgynous, genderqueer.

Transitioning for Transgender Persons

Some transgender people change their name, appearance, and other personal details (e.g., legal documents, gender identity in electronic medical records) to be more congruent and affirming of their gender identity. This is known as *transitioning* and there is no one, particular way that a person is expected to transition. Some transgender people may choose to socially transition by changing their clothes and behavior and use a preferred name. Others may medically transition via hormone therapy to alter their primary and/or secondary sex characteristics, as well as social appearance. A few may pursue surgical interventions to have their physical body coincide with their gender identity.

Others still may choose not to transition at all due to fear of rejection, discrimination, or safety concerns.

- **Gender Expression:** This refers to the external appearance and representation of a person's gender identity. This is usually expressed through behavior, clothing, haircut, voice, etc. and may or may not reflect societal gender norms and expectations. It should be noted that gender expression is not always consistent with gender identity.
- **LGBT = Lesbian, Gay, Bisexual and Transgender**
 - Acronym and umbrella term for diverse groups of sexual and gender minorities, including related identities such as queer
 - Lesbian refers to women with a same-sex sexual orientation
 - Gay more often refers to men with a same-sex sexual orientation but can also refer to women with a same-sex sexual orientation
 - Bisexual refers to persons with both same- and other-sex sexual orientation; that is, attraction to men and women
 - Transgender reflects gender minority status and does not imply a specific sexual orientation. Transgender Veterans may identify as straight, gay, lesbian, bisexual, etc.

Note about LGBT Usage in VA

VA uses LGBT in an inclusive way to reflect **ALL** sexual and gender minorities, including questioning, queer, intersex, asexual, two-spirit, gender non-conforming, and related identities. VA Serves All Who Served.

LGBT Veteran Prevalence Rates

The exact number of LGBT Veterans is unknown. Until recently, VA demographic data-collection systems did not collect data on gender identity. This new field has not been fully implemented and is not yet visible in the medical record. VA databases do not yet record sexual orientation identity; therefore, at present, we have no data for LGBT Veterans using VA services. However, research studies estimate the following:

- There are at least 1 million LGBT Veterans and 65,000 gay and lesbian active duty service members.
- Women are over-represented among sexual minority Veterans. 2.9% of active duty women identify as lesbian or bisexual compared to .6% of men who identify as gay or bisexual.
- There are approximately 15,450 transgender active duty men and women and at least 134,000 transgender Veterans.
- There are more than 6,000 transgender Veterans enrolled in VA care between 1996 and 2014 based on diagnostic codes.

Unique Cultural Considerations for LGBT Veterans

It is important to highlight the unique context that LGBT Veterans experience. There is a long history of bias against LGBT Service Members and Veterans. These populations have often experienced discrimination within both the larger civilian society and the military. Prior DoD policy said homosexuality was “incompatible” with military service. The most recent ban on LGB service was, “Don’t Ask, Don’t Tell”, a Department of Defense policy from 1994 to 2011 that prohibited openly LGB persons from serving in the military on the basis of their sexual orientation. Service members whose LGB transgenderisms and identities were discovered were discharged. DoD policy also banned transgender people from openly serving in the military. This policy was lifted June 2016 for current service members, though transgender new enlistees could not join the military until January 2018. Altogether, these DoD policies required LGBT Service Members to conceal and deny their sexual orientation and gender identity, for fear of harassment, violence, and discharge from service.

VA never banned care for LGBT Veterans. However, research suggests that LGBT Veterans anticipate discrimination from VA providers. In one study, 80% of LGBT Veterans endorsed hurtful and rejecting military experiences as the top barrier to LGBT Veterans using VA. Of note, 62% of LGB Veterans reported that none of their VA providers had asked about sexual orientation identity. Even when asked, 24% of these Veterans did not disclose their sexual identity to their VA provider. Further, a large majority of LGB Veterans were not aware of the relevance of their sexual orientation to their health and were fearful of disclosure.

Health Disparities

Minority Stress

Like other minority groups, LGBT people experience increased rates of physical and mental health conditions and barriers to accessing health care. The Minority Stress Theory can explain elevated rates of most health conditions in LGBT persons. According to this theory, sexual and gender minority identities are associated with increased stress including stigma, violence, discrimination, and identity concealment. Chronic stress is associated with poorer mental and physical health outcomes, such as depression, substance use, cancer, and obesity. LGBT people may feel excluded and discriminated against, which can lead to anxiety and depression as well as maladaptive ways of coping such as smoking, substance abuse, over eating, and not seeking healthcare when needed. At a societal level, anti-LGBT attitudes contribute to exclusion, lack of civil rights protections, difficulty accessing healthcare, and lack of training of healthcare professionals to treat LGBT people. In other words, LGBT health disparities are explained by the chronic stress of anti-LGBT attitudes and hostile social environments, and *not* by LGBT identities or behaviors themselves. Sexual orientation identity and gender identity are social determinants of health, like age, sex assigned at birth, race/

ethnicity, etc., that influence the individuals health beliefs, health behaviors, and ability to access health care.

Gay and Bisexual Male Veterans and MSM

Due to perceptions of stigma associated with identifying as gay, MSM are more likely to engage in secretive, anonymous, and unprotected sex with multiple partners. Consequently, MSM have an increased risk of HIV infection and transmission. MSM are less likely to get HIV testing and many women they might be sexually involved with are unaware of the fact that they have multiple sex partners and male partners; thus, these women are less likely to get HIV testing.

The prevalence of depressive disorders is substantially higher among cisgender men and transgender women who have sex with men, compared to cisgender men in the general population. People living with mood disorders, substance use disorders and serious mental illness or psychosis are disproportionately at risk for HIV acquisition and transmission. Similarly, high rates of major depression, anxiety, substance use, sexual and physical abuse, and suicidal behaviors have been documented in people engaging in same-sex sexual behaviors or identifying as gay.

Among gay male Veterans, research has found elevated risks of asthma, tobacco use, physical inactivity, and decreased likelihood of seeking health care due to cost. Higher rates of depression, PTSD, and alcohol abuse have also been found in gay male Veterans compared to heterosexual male Veterans.

Lesbian and Bisexual Female Veterans

Among a sample of female Veterans who served in the Iraq and Afghanistan conflicts, lesbian and bisexual Veterans reported higher rates of military sexual trauma (MST) and substance abuse but were more likely to report plans to use VA services. Compared to heterosexual female Veterans, lesbian and bisexual Veterans were also more likely to smoke and to have poorer mental and physical health outcomes. Higher rates of physical/sexual violence in childhood and adulthood and increased suicidal ideation have also been found among lesbian and bisexual female Veterans compared to their heterosexual counterparts. Intimate partner violence rates are also higher among sexual minority women Veterans compared to straight Veterans.

Transgender Veterans

Due to discrimination and stigma, many transgender individuals commonly live at the margin of society, with little access to resources. As a result, survival strategies like sex work increase the likelihood of exposure to violence, poor nutrition, and exposure to sexually transmitted diseases (STD). According to a study among U.S. Veterans, overall mortality rates among transgender Veterans was

9.3% over a 10-year period of follow up. Cause of death was similar to the cis-gender U.S.Veteran population with the exception of suicide rate. In one study of VA patients, transgender Veterans were 20 times more likely to engage in suicidal behavior than the general VA population. Moreover, rates of Gender Identity Disorder were 5 times higher among transgender Veterans seeking VA services than estimates for the general population. Another study in VA found worse mental and physical health outcomes for transgender Veterans compared with nontransgender counterparts on nearly every health condition examined. Further, African American transgender Veterans had higher rates of mental and physical health conditions and higher rates of incarceration and homeless than white transgender Veterans in VA. VA-using Veterans with transgender-related diagnoses who live in rural communities are more likely to smoke and have a PTSD diagnosis than transgender Veterans in urban areas.

Suicide Risk

LGBT individuals experience poorer mental health outcomes and higher suicide rates compared to heterosexual individuals. The same is true for LGBT Veterans. In a national probability sample, 47% of LGB Veterans reported a lifetime history of suicidal ideation (compared to 22% of heterosexual Veterans). Among transgender Veterans in an online survey, 66% reported a suicide attempt or plan and 57% reported suicidal ideation in the past year.

Resilience

Despite stigmatization, discrimination, and physical and mental health disparities, most LGBT people live healthy, productive lives, suggesting considerable resilience among this population. Many LGBT Americans view their LGBT identity as a positive aspect of their lives (34%) or as a neutral characteristic (58%). Among transgender Veterans, 26% report feelings of pride in their identity, fulfillment in living authentically, and feel they have overcome adversity related to marginalization and stigmatization.

Unique Primary Care Needs

HIV Prevention and Behavioral Change

Research on “safe sex fatigue” suggests that early after an HIV diagnosis, individuals may modify behaviors to be healthier and safer, both for themselves and their partners. However, as time progresses they may engage in riskier behaviors because they have become fatigued by the demanding behavioral and lifestyle changes. This has been found particularly among gay and bisexual men who report unprotected sex despite the risk for HIV/STDs.

What is Pre-Exposure Prophylaxis (PrEP)?

The CDC suggests that individuals who are at “substantial risk” of HIV exposure, but are currently HIV negative be considered for treatment. PrEP has been recommended for the following individuals considered at “substantial risk of HIV acquisition”:

1. Adult MSM/gay/bisexual men who engage in anal sex with partners of unknown HIV status without 100% condom use. (Condom use is not necessary in monogamous relationships with HIV negative partners);
2. Adult intravenous drug users (IVDU);
3. Anyone who has tested positive for an STD within the past 6 months;
4. Anyone whose sexual partners are HIV positive (this is known as sero-discordant partnerships);
5. Adult woman with HIV and pregnancy plans, without protecting the uninfected partner during conception;
6. Adults reporting multiple sexual partners.

The existing literature supports the use of PrEP for HIV prevention among HIV negative people. In a multinational study called the Pre-Exposure Prophylaxis Initiative, researchers studied the safety and effectiveness of PrEP in gay and bisexual men, and among those with detectable levels of PrEP in their system (i.e., were adherent to the medication), PrEP reduced the risk of HIV infection by as much as 92%.

Create a Welcoming, Inclusive Environment for LGBT Veterans

Many LGBT patients avoid or delay medical care due to receiving inappropriate or inferior health care related to experienced or anticipated discrimination and stigmatization by health care providers and institutions. One way to combat LGBT stigma is to make the healthcare setting a welcoming and safe environment for LGBT Veterans. Below are some suggestions for doing so:

- Know that all VA employees are required to create a welcoming environment for LGBT Veterans. See **VHA Directives 1340 and 1341**, (https://www.va.gov/vhapublications/ViewPublication.asp?pub_ID=6431 and https://www.va.gov/vhapublications/ViewPublication.asp?pub_ID=5438) for updates.
- Display the VA non-discrimination policies (including visitation of designated family – whomever the Veteran identifies as family) and patient’s bill of rights.
- Display materials and signage that reflect and are inclusive of LGBT Veterans and their families (e.g., rainbow flags, LGBT-friendly symbols, visuals of same-sex couples, brochures for LGBT health). Also, acknowledge rel-

evant days of observance (e.g., World AIDS Day, LGBT Health Awareness Week, LGBT Pride Month, National Transgender Day of Remembrance).

- Avoid assumptions about sexual orientation and gender identity. Use open-ended questions and gender-neutral language. For example, ask about the Veteran’s partner or significant other (versus girlfriend, husband).
- Take a non-judgmental, open-minded, and empathic approach with all Veterans to foster rapport and trust.
- Be aware of misconceptions, bias, stereotypes, and communication barriers. For example, avoid labeling sexual behavior as promiscuous, dangerous, immoral, or referring to someone’s identity as “confused,” a “phase,” a “lifestyle” or a “preference.”
- Be aware that sexual orientation identity does not always align with sexual behavior.
- Facilitate disclosure of the Veteran’s LGBT status but also be aware that disclosure is an individual process. Honor and respect the Veteran’s pace and decision-making.
- Review the GLMA resources on care for LGBT patients http://glma.org/data/n_0001/resources/live/GLMA%20guidelines%202006%20FINAL.pdf

Specific Needs of Lesbian and Bisexual Female Veterans

Social and Behavioral Risk Factors	Screening and Health Concerns
Stigmatization due to sexual orientation/gender expression	Colon cancer
Avoidance or underutilization of medical care	Depression
Lack of health insurance	Diabetes
Obesity/being overweight	Fertility and pregnancy
Tobacco, drug, alcohol use	Mammograms
Chronic pain	PAP smear
Hypertension	STD/HIV
Intimate partner violence	-
Sexual assault/MST	-

Specific Needs of Gay and Bisexual Male (including MSM) Veterans

Social and Behavioral Risk Factors	Screenings and Health Concerns
Stigmatization due to sexual orientation/ gender expression	Eating disorders
Tobacco, drug, alcohol use	Anal cancer secondary to HPV
Depression, anxiety	Hepatitis immunizations
False assumption regarding HIV prevention/ treatment	Intimate partner violence

Unique Primary Care Needs of Transgender Veterans

As with all Veterans, interdisciplinary care (e.g., primary care, mental health, etc.) and communication among team members is recommended for transgender Veterans seeking treatment. For transgender Veterans who are seeking hormone therapy, a mental health provider must first diagnose Gender Dysphoria, and ensure that they understand the risks and benefits of hormone therapy (informed consent). Veterans who are seeking hormones may request hormone therapy and providers must follow Pharmacy Benefits Management (PBM) guidelines to dispense.



EVALUATION

Assessing Sexual Identity and Gender Identity

Per VHA Directives (1340 and 1341), all staff provide equitable, respectful, and affirming clinical care appropriate to LGBT Veterans. This includes treating LGBT Veterans with respect and dignity. Furthermore, a sexual health assessment should be conducted with all Veterans and attention be given to LGBT health disparities.

Why and how you ask about sexual orientation identity and gender identity matter.

- Provide context and a clear rationale for why you are asking.
- Inform Veterans that you ask all patients questions about sexual orientation identity and gender identity.
- Try not to make assumptions.
- Assure the Veteran that their information is confidential.
- Emphasize to Veterans that sexuality and sexual health are an important part of a high quality, regular medical exam or physical history.
- Based on the Veteran's sexual and gender identities, do the appropriate health assessments based on population risk.

- Conduct assessments of sexual orientation identity, gender identity, and sexual health at initial intake and then to re-assess annually, not at every visit.
- Attend to the responses the Veteran provides; e.g., if the Veteran reports being a lesbian and only engaged in same-sex sexual behavior, it may not be relevant or appropriate to then ask about prevention of pregnancy, but pregnancy planning may be important.

Having good rapport with a Veteran is important. It can help to start with more general questions and then find an opportunity (e.g., when Veteran is talking about relationships or social support) to ask questions related to sex, sexuality, and gender identity. When asking about sexual orientation identity, providers may want to offer “gay/lesbian” or “bisexual” as first options, rather than “heterosexual”, to convey that you expect and welcome LGB Veterans in your clinic. Also, acknowledging that these conversations can be awkward and uncomfortable can be validating to Veterans and allow them to ask questions of you as well. For training on how to ask patients about sexual orientation identity, see “*Do Ask, Do Tell: 5 Awkward Minutes to Better Patient Care*” in the VA Talent Management System (TMS).

Interestingly, healthcare providers are overly concerned about offending patients by asking about sexual orientation and gender. In a large study of physicians and patients, 80% of providers worried that patients will be offended if they are asked about sexual orientation and gender identity. However, only 11% of patients said they might be offended if asked by their healthcare provider. Data shows that Veterans are just as willing to answer questions about sexual orientation and gender identity as non-Veterans.

Sexual Health Assessment

As part of a comprehensive sexual health assessment, the CDC recommends the “5 P’s” for taking a sexual history. For *A Guide to Taking a Sexual History*, see <https://www.cdc.gov/std/treatment/sexualhistory.pdf>.

- **PARTNERS** – the number and gender of Veteran’s sex partners; never make assumptions about a Veteran’s sexual orientation or the sex of their partners.
 - If there is 1 sex partner over the past 12 months, inquire about the length of that relationship and the partner’s risk factors (e.g., current/past sex partners, drug use).
 - If more than 1 partner is reported in the past 12 months, inquire about risk factors (e.g., condom use/non-use, partner risk factors).
- **PRACTICES** – ask about the Veteran’s sexual behaviors over the past 12 months (e.g., genital, anal, oral) with each partner.
- **PROTECTION from STDs** – explore the Veteran’s abstinence, monogamy, condom use, and perception of their risk and partner’s risk to STDs, including HIV; also, testing for STDs and HIV.

- **PAST history of STDs** – assess if the Veteran has ever been diagnosed with an STD or HIV, when, and how they were treated; inquire about partner’s STD history and testing, including HIV.
- **PREVENTION/PLANNING of pregnancy** – ask about the Veteran’s plans to become pregnant or father children. Conversely, also ask plans to avoid unwanted pregnancy, including birth control and contraception.

Assessing for LGBT Health Disparities

Based on the population-based LGBT health disparity research, clinicians should generally assess LGBT Veterans for depression, suicidal ideation, anxiety, substance use disorder (including alcohol and tobacco), trauma and PTSD (including intimate partner violence), although each assessment should be individualized. Please refer to the Unique Primary Care Needs section regarding specific domains to assess for LGBT Veterans.

Assessing for Gender Dysphoria

Veterans who identify as transgender or gender non-conforming may also experience gender dysphoria, which refers to distress that may accompany the incongruence between one’s assigned sex at birth and one’s gender identity. The DSM-5 diagnosis of Gender Dysphoria was previously known as Gender Identity Disorder in DSM-IV and continues to be referred as such in ICD-10 encounter codes.

Pages 259-260 were removed due to copyright permissions. See the printed manual or American Psychiatric Association Diagnostic and Statistical Manual Criteria for Dysphoria in Adolescents and Adults.

<https://www.psychiatry.org/psychiatrists/practice/dsm>

LGBT Veteran Services

Given the increased health risks, health disparities, and unique challenges in accessing quality healthcare, the following are various LGBT-affirming services offered by VA to ensure a welcoming environment for LGBT Veterans and guidance and education to VA providers regarding LGBT health issues. An LGBT Veteran Care Coordinator is available at every medical center to assist LGBT Veterans who need services, identify and address gaps in clinical services for LGBT Veterans, educate VA staff, and work to ensure the VA environment is welcoming. To find the LGBT Veteran Care Coordinator at your facility, go to <http://www.patientcare.va.gov/LGBT/VAFacilities.asp>.

Psychotherapy Services

HIV Psychotherapy

For LGBT Veterans who are newly diagnosed with HIV/AIDS or those who are struggling with HIV-related concerns (medical, behavioral, social, or emotional), individual psychotherapy may be beneficial. Psychotherapy is brief and time-limited in nature. Often, interventions involve psychoeducation and teaching Veterans strategies that target stress management, coping with stigma and discrimination (related to HIV/AIDS status and LGBT status), behavioral manage-

ment of disease (e.g., medication adherence), substance use, comorbid mental health concerns, and commitment to change. In addition, same-day, walk-in appointments are available for acute mental health concerns.

PrEP Psychotherapy

For Veterans without HIV who are at risk of HIV infection from sex with an HIV-positive partner or injection drug use, PrEP may be warranted. See **PrEP for Sexual and Drug Partners**, p. 81. Counseling is available to assist the Veteran in finding ways to improve medication adherence (e.g., using a pillbox, setting reminders, phone alarms) and to assist with addressing psychosocial and behavioral contraindications to PrEP candidacy. Psychotherapy can offer psychoeducation (e.g., related to HIV risk and acquisition) and brief interventions for mood disorders, substance use disorders, and health behavior change (e.g., increase safe sex practices) to increase candidacy.

LGBT-Affirmative Individual Psychotherapy

VA offers therapy with mental health clinicians who are familiar with LGBT issues. Clinicians help those LGBT Veterans who want to transition work towards individual goals related to identity, with a focus on emotional well-being, positive identity and self-acceptance, empowerment, and self-advocacy.

Group Psychotherapy and Support Groups

VA offers group psychotherapy and support services for LGBT Veterans. These may include psychoeducational groups with a particular topic (e.g., transgender health) or less structured groups that focus on broader concepts related to LGBT identity (e.g., identity development, intimacy and relationships, minority stress, stigma, homo/transphobia, discrimination, acceptance, developing a positive LGBT identity and resiliency) or treatment for a particular condition (e.g., smoking cessation, PTSD) with tailoring of the group to be culturally responsive to LGBT Veterans. LGBT persons in general are likely to experience negative social outcomes including rejection by family, friends, and significant others, and sometimes employment or housing discrimination and other negative societal level events. LGBT Veterans, moreover, likely experienced anti-LGBT discrimination during their military service and as a result may have fewer social connections with Veterans and others. Thus, given the stigma and marginalization of LGBT Veterans, group psychotherapy can be especially beneficial for some in building a supportive community and a positive social network.

Peer Support

VA offers LGBT peer support specialists, who are fellow Veterans who identify as LGBT. LGBT peer support specialists may be able to connect to other LGBT Vet-

erans in a way that fosters camaraderie, trust, and understanding. Peer support specialists can also help LGBT Veterans navigate the VA system and advocate for themselves in their health care (e.g., know their patient rights, anti-discrimination policies).

Mental Health Evaluations for Hormone Therapy

Before transgender Veterans initiate masculinizing or feminizing hormone therapy as part of medical transition, a mental health evaluation is needed to establish or verify a Gender Dysphoria diagnosis and determine that they are competent to make an informed medical decision. These evaluations also typically include evaluation of the Veteran's transition goals and suggestions to maximize success. Eligibility is then communicated to the prescribing clinician, who initiates hormone therapy and monitors until a therapeutic dose has been reached. These mental health evaluations are typically conducted at some facilities by a psychologist or a psychology resident or other mental health professional.

Rx MANAGEMENT

Hormone Therapy for Gender Transitioning

The general approach of hormone therapy for both adult transgender women and men consists of suppressing the primary and secondary natal sex characteristics in the patient and enhancing the sex characteristics that are congruent with the patient's gender identity and transition goals. Hormone therapy is also sometimes utilized to generate a more gender neutral appearance.

The Department of Veterans Affairs Pharmacy Benefits Management (PBM) Services provides the most up-to-date VA Directives on its website. See www.pbm.va.gov/.

Potential ARV Interactions

Medication	Antiretroviral	Interaction
Estradiol	<ul style="list-style-type: none"> • Tipranavir • Atazanavir/cobicistat • Ritonavir • Efavirenz • Etravirine 	<ul style="list-style-type: none"> • P-glycoprotein/ABCBI inhibitors (e.g. ritonavir) may ↑ the serum concentration of P-glycoprotein/ABCBI substrates such as estradiol • Estrogen derivatives may enhance the dermatologic adverse effect of tipranavir; tipranavir may ↓ the serum concentration of estrogen derivatives

		<ul style="list-style-type: none"> • Atazanavir has been shown to ↓ the metabolism of estradiol • Moderate CYP3A4 inducers efavirenz and etravirine may ↓ the serum concentration of estradiol
Medroxyprogesterone Acetate	<ul style="list-style-type: none"> • Amprenavir • Atazanavir • Cobicistat • Darunavir • Delavirdine • Efavirenz • Etravirine • Elvitegravir • Fosamprenavir • Indinavir • Lopinavir • Nevirapine • Ritonavir • Saquinavir • Tipranavir 	<ul style="list-style-type: none"> • Oral atazanavir may ↑ the serum concentration of progestins; medroxyprogesterone acetate depot injection does not appear to interact • Darunavir, efavirenz, nevirapine, and saquinavir may ↓ the serum concentration of progestins • Lopinavir may either ↓ or ↑ the serum concentration of progestins; excluding medroxyprogesterone acetate depot injection • Tipranavir and/or cobicistat may ↑ serum concentration of progestins • Moderate CYP3A4 inducers (etravirine) may ↓ the serum concentration of progestins • Strong CYP3A4 inhibitors (nevirapine, indinavir, ritonavir) may ↑ the serum concentration of medroxyprogesterone acetate • Delavirdine may ↑ or ↓ serum concentration of progestins when administered together • Elvitegravir may ↑ serum concentration of progestins when administered together
Testosterone	No contraindications or major drug-drug interactions with ARV therapy	
Spirolactone	No contraindications or major drug-drug interactions with ARV therapy	

Please see **PrEP for Sexual and Drug Partners**, p. 81 for information on pharmacotherapy.

Lesbian, Gay, Bisexual and Transgender (LGBT) Health Program

In 2012, the Office of Patient Care Services created the LGBT Health Program (10P4Y), which provides policy recommendations, provider-education programs, and clinical services to support personalized, pro-active, patient-driven health-care for LGBT Veterans. For more information about the LGBT Health Program,

email at VALGBTProgram@va.gov or visit <https://www.patientcare.va.gov/LGBT/index.asp>.

LGBT Veteran Care Coordinators

Every VA medical center has an identified LGBT Veteran Care Coordinator (VCC) who:

- Assesses clinical needs for LGBT-specific services
- Develops services for LGBT Veterans (e.g., support groups, hormone evaluations)
- Provides education or training to VA staff
- Publicizes community LGBT resources in VA
- Outreaches to LGBT community organizations

To find your local LGBT Veteran Care Coordinator, visit <https://www.patientcare.va.gov/LGBT/VAFacilities.asp>.

LGBT Policy, Trainings, and Resources

LGBT Affirming VHA Directives and Policies

- VHA Directive 1340 (Provision of Health Care for Veterans who Identify as Lesbian, Gay, or Bisexual) https://www.va.gov/vhapublications/ViewPublication.asp?pub_ID=5438
- VHA Directive 1341 (Providing Health Care for Transgender and Intersex Veterans) https://www.va.gov/vhapublications/ViewPublication.asp?pub_ID=6431
- Rights and Responsibilities of VA Patients and Residents of Community Living Centers <https://www.va.gov/health/rights/patientrights.asp>
- Rights and Responsibilities of Family Members of VA Patients and Residents of Community Living Centers <https://www.va.gov/health/rights/familyrights.asp>

Transgender Veteran Related Trainings

- TMS Trainings:
 - An Introduction to Transgender Care
 - Transgender Mental Health Services
 - Transgender Health: Prescribing Cross Sex Hormones
 - Two New Fields: Birth Sex and Self-Identified Gender Identity
 - Self-Identified Gender Identity (SIGI) SharePoint: <http://go.va.gov/SIGI>
- Transgender Education SharePoint: <http://go.va.gov/Transgender>

LGB Veteran and Sexual Health Related Trainings

- TMS Trainings:
 - Do Ask, Do Tell: 5 Awkward Minutes to Better Patient Care
 - Do Ask, Do Tell: Assessing Sexual Health of LGBT Veterans (and Everyone Else)
- Do Ask, Do Tell: LGB Veteran Health Care LGB Education SharePoint: <http://go.va.gov/LGB>



WHEN TO REFER

If a Veteran identifying as lesbian, gay, or bisexual is in need of mental health treatment or support, PCMH and specialty mental health services are available, as noted above. For transgender Veterans specifically, the roles of the mental health provider are to provide routine MH care, establish the diagnosis of Gender Dysphoria and evaluate the Veteran's capacity to make an informed medical decision. Suggestions for ways to maximize success on hormone therapy or with surgical interventions (outside VA) may also be offered. The role of the primary care provider is to be informed of risk factors experienced by LGBT Veterans, assess potential risks, and initiate prevention or treatment. While experienced primary care providers can prescribe hormone therapy, endocrinologists may be consulted to initiate hormone therapy after the Veteran has received a Gender Dysphoria diagnosis.



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KEY POINTS

- Hospice and Palliative Care collectively represent a continuum of comfort-oriented and supportive services provided in the home, community, outpatient, or inpatient settings to address advanced disease states and end-of-life issues in patients with HIV/AIDS.
- Hospice is a mode of palliative care, often associated with specific characteristics of the individual receiving the care: diagnosed with a known terminal condition with a prognosis less than 6 months and desiring therapies with a palliative intent for the terminal condition.
- Palliative care is a broader term that includes hospice care, as well as other care that emphasizes symptom control, but does not necessarily require the presence of an imminently terminal condition or a time-limited prognosis. Palliative care may include a balance of comfort measures and curative interventions that varies across a wide spectrum.
- VA benefits cover both hospice and palliative care services.



BACKGROUND

The field of HIV/AIDS medicine has been dramatically transformed from its beginning in the early 1980s. For the first 15-plus years of the HIV epidemic, the disease was inevitably progressive without fully effective treatments to maintain viral suppression. This led to most patients progressing to end-stage AIDS, and ultimate death from multiple different opportunistic infections (OIs). Hospice and palliative care became a mainstay in this field, with clinicians needing to have a facile understanding when and how to transition a patient to comfort care at the end of their disease process. As highly-active antiretroviral (ARV) therapy evolved and matured from the late 1990s to the present day, the vast majority of patients began living with HIV and not progressing and dying. Dedicated AIDS hospice programs around the country became unnecessary and closed down or changed focus, and the field moved toward keeping patients healthy and stable and virologically suppressed.

ARV therapy was a phenomenal medical advance; however, an understanding of when and how to use hospice and palliative care options in patients with HIV in the current era is still important. There are still subsets of patients with HIV who for various reasons still progress to advanced/end-stage AIDS. Situations include those who are still not diagnosed until at a very advanced state of AIDS, sometimes with untreatable OIs and malignancies, and those patients who are unable to maintain adherence to ARV therapy due to multiple psychosocial issues (such as substance abuse and severe mental health issues) and unfortunately progress to an end-stage situation. Also, in the current era we are understanding more

Note: Some medications mentioned in this chapter may not be available on the VHA National Formulary (<https://www.pbm.va.gov/NationalFormulary.asp>). Consult VA pharmacists for alternatives.

about the still-higher rate of death from other processes other than OIs, such as malignancies, liver failure, early cardiovascular disease, and other complications of multiple aging comorbidities from decades of living with HIV infection. This can make it especially challenging clinically in terms of deciding if and when a patient is appropriate for full hospice care, or a blend of palliative care and ongoing treatment.

There has been some interesting modeling work using the Veterans Aging Cohort Study (VACS) Index to more accurately estimate mortality risks in patients with HIV. Earlier estimate models emphasized classic AIDS-specific issues such as OIs, CD4 count, and HIV viral load. Since in the current era mortality is often due to additional co-occurring issues, the VACS Index reflects the increasing role of multi-organ system injury and HCV coinfection. The VACS Index incorporates age and routine laboratory tests: CD4 count, HIV viral load, hemoglobin, platelets, AST, ALT, creatinine, and HCV status. The generalizability of the VACS Index has been demonstrated in a large independent sample of patients on ARV therapy, over differing periods of ARV therapy exposure and among important subgroups of patients. Using the VACS Index may help guide hospice decision making and timing in certain clinical situations. Further information, including the VACS calculator, can be accessed at: <https://medicine.yale.edu/intmed/vacs/welcome/vacsindexinfo.aspx>.

Hospice Care

VA defines hospice as a mode of palliative care, often associated with specific characteristics of the patient receiving the care: diagnosed with a known terminal condition with a prognosis less than 6 months and desiring therapies with a palliative intent for the terminal condition. Hospice care can be delivered in a dedicated inpatient hospice unit, or, more commonly now, in the home, if a patient has an adequate living situation, caregiver help, and psychosocial support. Traditionally, hospice care is begun when there is clearly an end-stage disease process occurring, with an estimated life expectancy of six months or less. As noted above, in the HIV/AIDS field it can be more challenging than ever deciding when to consider hospice care. What used to be considered an end-stage AIDS situation with, for example, advanced wasting and one or more active OIs, could now potentially be a situation where recovery is expected if a patient has not been in active care with ARV therapy and is willing and able to access treatment. Most commonly in the current era, hospice care is considered due to non-OI situations, such as advanced/untreatable malignancies, end-stage liver disease, or other clearly end-stage health situations.

Once hospice care is agreed to by both the medical providers and the patient/family as the most appropriate course of action, the focus of care becomes more holistic rather than a traditional disease/treatment model. Hospice care excels at giving patients comfort, dignity, and personal growth at life's end. This encompasses biomedical, psychosocial, and spiritual aspects of the dying experience, emphasizing quality of life and healing or strengthening interpersonal relation-

ships rather than prolonging the dying process at any cost. A quality hospice program comprises an interdisciplinary team of experts that deals with all aspects of the dying process.

One unique aspect of hospice care in the HIV/AIDS setting is the decision of when to continue or stop the use of ARV therapy. Sometimes, it is a requirement of hospice programs due to the payor source that ARV therapy be discontinued given its relatively high cost, and this can sometimes be a very difficult decision for patients, who have often been conditioned to maintain perfect adherence to long-term ARV therapy. If ARV therapy is clearly not going to impact the end-stage disease course and especially if continuing ARV therapy is causing any type of ongoing and unnecessary side effects, it may be appropriate to stop. Ideally, this would be decided on a case-by-case basis between the clinician and the patient, not just as an insurance mandate.

For patients in the VA system, hospice care is part of the VA Standard Medical Benefits Package; all enrolled Veterans are eligible if they meet the clinical need for the service. This is available when a patient has a terminal condition, has less than six months to live, and is no longer seeking active treatment other than palliative care. Hospice care in the VA system can be provided at home, in an outpatient clinic setting, or in an inpatient setting if warranted. VA hospice care approaches relief of suffering and symptom control in a way that respects the patient's personal, cultural, and religious beliefs and practices. VA provides home hospice and bereavement services through community hospice agencies, and a care team approach—a plan of care will be developed to meet the patient's medical, social, spiritual and psychological needs. Details specific to VA patients can be found on the Department of Veterans Affairs, https://www.va.gov/geriatrics/guide/longtermcare/Hospice_Care.asp.

Palliative Care

The goal of palliative care, per the World Health Organization definition, is to improve the quality of life for patients facing the problems of life-threatening illness through the prevention and relief of suffering. In addition to symptom control, Palliative Care has a major focus on communication skills. The VA National Ethics Center provides training for Goals of Care Conversations. For more information, see <https://www.ethics.va.gov/LST/IntroductionToElicitingValuesGoals.pdf>.

The National Center for Ethics is also leading the Life-Sustaining Treatment Decisions Initiative (LSTD) as a national VA quality improvement project with the aim to promote personalized, proactive, patient-driven care for Veterans with serious illness by eliciting, documenting, and honoring their values, goals, and preferences. For more information, see <https://www.ethics.va.gov/LST.asp>.

Palliative care can be provided in conjunction with other therapies intended to prolong life, such as chemotherapy, radiation therapy, or major surgical or medical interventions.

The focus of palliative care is to alleviate ongoing or severe symptoms that may accompany a disease state or the treatment thereof, with a focus on symptom control and quality of life for the patient. This approach also includes psychosocial and spiritual support for the patient and affected family members. This often requires a multidisciplinary team approach, between treating specialists, primary care providers, and palliative care specialists. The therapeutic approach to some common symptoms encountered in palliative care are addressed below.

Pain

Uncontrolled pain is one of the most common fears of patients dealing with an advanced disease process, and deserves great attention. There are many medication approaches to pain control, and a detailed reference is the WHO Cancer Pain Relief guidelines. Opiate therapy is the most recognized option for pain control. Some studies suggest that oxycodone or fentanyl may be better tolerated than morphine. Other classes of medications also serve an important role in pain control, including NSAIDs, neuropathic pain medications, corticosteroids, anxiolytics, antidepressants, and cannabinoids (**Table I**). Depending on the clinical situation, routes other than oral administration may be necessary, such as sublingual, transdermal, subcutaneous, and intravenous. A provider in this situation should become adept with the use of the many different options and combinations of treatment, using a pain specialist when needed for particularly difficult circumstances. For more information, see <https://www.va.gov/painmanagement/>.

Table I. Pain Medications Useful in Palliative Care

Opiates (can be given PO/SL/TD/IM/SC/IV)	Medications for Neuropathic Pain	Adjuvant Treatments
morphine hydromorphone oxycodone codeine methadone fentanyl oxymorphone	tricyclic antidepressants gabapentin pregabalin carbamazepine valproic acid duloxetine	NSAIDs acetaminophen muscle relaxants benzodiazepines corticosteroids lidocaine (topical) cannabinoids focal radiation acupuncture

Nausea

Cyclical, persistent, or intractable nausea is another common symptom that can be very distressing, and relieving this symptom can markedly improve quality of life as well as the ability to receive optimal nutrition and other needed medications. If possible, finding and eliminating or treating the source of the nausea is optimal, but often the cause can be elusive or multifactorial. See **Table 2**.

Nevertheless, in one study of 61 hospice patients, the cause of nausea was established for 75% of cases. The most frequent causes were chemical abnormalities (metabolic, drugs, infection; 33%), gastric stasis (44%), and visceral causes (bowel obstruction, gastric bleeding, enteritis, constipation; 31%). Nonpharmacological approaches to nausea include: avoiding strong odors; eating small, frequent meals; limiting oral intake during periods of severe nausea; and relaxation techniques.

Table 2. Clues to Specific Causes of Nausea based on History and Physical Exam (modified from Wood et al.)

Pattern of Nausea	
Large volume, infrequent vomitus relieves nausea	Partial or complete bowel obstruction
Small-volume emesis	Gastric stasis
Symptoms Associated with Nausea	
Vertigo, nausea associated with movement	Vestibular dysfunction
Morning nausea, with headache, neuro symptoms	Increased intracranial pressure
Polyuria, polydipsia	Hyperglycemia, hypercalcemia
Altered mental status	Uremia, hypercalcemia, increased intracranial pressure
Neck stiffness	Meningeal disease
Syncopal episodes, early satiety	Autonomic insufficiency
Decreased frequency of bowel movements; Hard stools, straining with defecation	Constipation
Obstipation, crampy abdominal pain	Bowel obstruction
Bloating, early satiety	Gastric stasis
Heartburn, worse with lying down	Gastroesophageal reflux disease
RUQ pain	Gallbladder or Liver Disease
Epigastric pain, radiating to back	Pancreatitis
Fever, diarrhea	Gastroenteritis
Emotional responses	Anxiety
Exam Findings	
Orthostatic bp/pulse changes	Autonomic insufficiency
Papilledema/neurologic signs	Increased intracranial pressure
Thrush/herpetic lesions	Oropharyngeal/esophageal irritation
Abdominal distension, abnormal bowel sounds	Ileus, constipation, bowel obstruction

Abdominal masses, ascites	Abdominal malignancy
Splenomegaly	Bowel compression by spleen
Fecal impaction	Constipation

There are multiple classes of antiemetics (**Table 3**). Initially, a first line agent is used and titrated as needed, but if symptoms persist another agent that antagonizes a different nausea pathway should be added. Adding a second agent is preferred to switching because nausea is often multifactorial. A common management error is that first-line antiemetics are given on an as-needed basis instead of being scheduled. In one uncontrolled study, prochlorperazine was more effective than oral ondansetron alone or with additional antiemetics. Dosing of antiemetics prior to known emetogenic triggers, such as certain medications (i.e., opiates) or activities, may be helpful.

Table 3. Antiemetic Classes, Agents, Applications, and Potential Pitfalls

Antiemetic Class	Agents	Applications; Pitfalls
Dopamine D2 receptor antagonists	Metoclopramide, prochlorperazine, haloperidol, olanzapine	First-line in general and for opiate-induced nausea; may be sedating
5HT3 serotonin receptor antagonists	Ondansetron, granisetron, palonosetron, dolasetron, tropisetron	Chemotherapy, radiation, post-operative; possibly for opioid-induced and in uremia; may aggravate constipation; may prolong QT-interval; dose-adjust in hepatic impairment
H1 histamine receptor antagonists	Diphenhydramine, dimenhydrinate, doxylamine, meclizine, promethazine, hydroxyzine	Especially useful in vertigo-induced nausea; Promethazine can be given po, IM or per rectum; do not give IV; Promethazine may aggravate opiate-induced nausea
Acetylcholine receptor antagonists	Chlorpromazine, promethazine, hyoscine	For anxiety, increased intracranial pressure; may cause sedation, hypotension
Cannabinoid receptor agonists	Dronabinol, nabilone	For nausea unresponsive to other agents; may also stimulate appetite; may cause dizziness, sedation, confusion

Benzodiazepines	Lorazepam is preferred	For anxiety; may potentiate activity of other antiemetics; may cause sedation, confusion
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Many of the drugs in the table, such as olanzapine, may act on multiple receptors.

Dyspnea

This can be another very distressing symptom both for the patient and the family. It may be a result from the underlying disease process (malignancy, pulmonary OI, or COPD/CHF), or a symptom seen at end of life in a classic hospice situation. Causes are highly variable, and treatment should be directed to the root cause when possible. Aside from usual pulmonary treatments such as oxygen and bronchodilators for true hypoxia, other potentially beneficial treatments include diuretics (if needed), corticosteroids, and anxiolytics. Especially in end-stage hospice situations, the sensation of ‘air hunger’ has been shown to be relieved by opiates. To reduce tracheal secretions, anticholinergics, available for subcutaneous administration if necessary, may be useful. These agents include glycopyrrolate (preferred agent if sedation is not desired), atropine (sedating), scopolamine (sedating), hysocine butylbromide, and hysocine hydrobromide. For the “death rattle” at the end of life, place the patient on their side, reposition to the other side every 3-4 hours, elevate the head of the bed slightly, provide frequent mouth care, and use the anticholinergics, as above.

Delirium

This is defined as a transient disorder of cognition and attention, often accompanied by the disruption of the normal sleep-wake cycle. The causes are diverse, and can include metabolic disturbances, infection and fever, hypoxia, CNS insults, and drug side effects. Management should be directed at the suspected cause when possible. Interventions to improve sleep quality may reduce delirium. In some cases, sedation may be necessary to alleviate severe agitation. In end-stage situations, an agitated delirium termed ‘terminal restlessness’ can occur; benzodiazepines are commonly used in this situation.

Depression, Fatigue, and Sleep Disturbance

These are all common and often interrelated symptoms that can often be effectively addressed in palliative care. Recognizing and treating these symptoms can go a long way to improve quality of life throughout the disease process. Patients may have better daily functioning and interactions with loved ones if these issues can be treated. Standard antidepressant medications may be instituted, as well as other psychopharmacologics as needed. Psychostimulants (methylphenidate or dextroamphetamine) have been studied in the palliative care setting and have been found to be effective in treating depression, fatigue, and opioid-induced sedation.

In one study of Veterans in hospice, poor sleep quality was common and older age, depression, and having a caregiver other than a spouse/partner were contributing factors. Uncontrolled physical symptoms (i.e., pain, nausea, and dyspnea) and anxiety were the most common causes of insomnia in hospice patients. The treatment of insomnia in the hospice setting is poorly studied; in one study of hospice patients, temazepam was more effective than zolpidem. Melatonin has also been advocated.

Constipation

This is another common symptom requiring treatment in the palliative care setting. Many causes should be considered and addressed, including dehydration, the underlying disease process, mechanical obstruction, oral intake and dietary issues, and medication side effects. Managing dehydration effectively is important to help prevent this symptom. Using all available classes of laxatives and escalating as needed is helpful—including bulk-forming (psyllium), osmotic (lactulose, polyethylene glycol), stimulant (senna, bisacodyl) and stool softener (docusate) medications. Anticipating constipation as opioids are escalated in the palliative setting is important, and adding laxatives (typically a stimulant and/or osmotic agent(s)) early on to prevent constipation should be routinely implemented. Methylnaltrexone, naloxegol, alvimopan, lubiprostone, and linaclotide, are newer agents specifically approved to treat opioid-induced constipation.

Xerostomia (Dry Mouth) and Oral Discomfort

Symptoms of dry mouth or oral mucosal breakdown are common in hospice patients, and have varying causes. Often in end-stage AIDS, infections contribute to this problem, and should be treated appropriately; for example, antifungals for oral candidiasis and antivirals for HSV ulceration. Painful aphthous ulcers can be treated by topical corticosteroid solutions and local analgesic agents, such as viscous lidocaine. Many classes of drugs promote xerostomia, including opiates, NSAIDs, proton pump inhibitors, corticosteroids, diuretics, antidepressants, antipsychotics, antihistamines, H₂ blockers, benzodiazepines, calcium channel blockers, and beta-blockers. Xerostomia also correlates with anorexia and the severity of other oral symptoms, including oral discomfort, dysgeusia, dysmasesia (difficulty chewing), dysphagia, and dysphonia. Xerostomia may be alleviated by stopping the offending drug (although this is often not possible), salivation stimulants (sugar-free chewing gum, pilocarpine), or with artificial saliva. Mucin-based artificial saliva sprays (e.g., Saliva Orthana) are more effective than those based on carboxymethylcellulose. For general oral discomfort in the palliative setting, humectant (non-alcohol) mouthwashes, hydration with ice chips or popsicles, and oral hygiene using glycerin mouth swabs may provide comfort.

Hiccups

Persistent or refractory hiccups can be a cause of discomfort, and can have many causes. Promoting gastric emptying with metoclopramide may help. Treating esophagitis, a common cause of hiccups in advanced AIDS, can be done with antifungals, antivirals, and acid suppressants, as appropriate. The only FDA-approved drug for hiccups is chlorpromazine. However, there are small case series showing effectiveness of other agents and individual patients may respond better to one of these, such as muscle relaxants (baclofen in particular), anticonvulsants (phenytoin, gabapentin, carbamazepine), olanzapine, or amitriptyline.

Pruritis

Pruritis is another common and occasionally severe symptom, and may be due to dry skin, dermatologic conditions (eczema, contact dermatitis, papular pruritic eruption, eosinophilic folliculitis, psoriasis, seborrhea, prurigo nodularis), infections (dermatophytosis, impetigo, folliculitis), organ dysfunction (cholestasis, hyperthyroidism, chronic kidney disease), malignancy (lymphoma), neuropathy, psychiatric conditions (substance abuse, obsessive-compulsive disorder), or induced by opioid use. The treatment of pruritus should be directed at the underlying cause, if possible. Directed treatment includes emollients for dry skin and topical corticosteroid creams, calamine lotion, and pramoxine creams. Sedating antihistamines (e.g., hydroxyzine, doxepin, and diphenhydramine), corticosteroids, and SSRIs may be of benefit. In the setting of end stage liver disease, oral cholestyramine to reduce elevated bile acids may alleviate severe pruritis. For cholestatic and psychogenic itching, antidepressants such as mirtazapine, paroxetine, and sertraline may be helpful. For neuropathic itching, gabapentin, pregabalin, capsaicin, pramoxine cream, and lidocaine/prilocaine cream may be beneficial. Gabapentin may also alleviate the pruritis associated with kidney disease. Topical calcineurin inhibitors (tacrolimus, pimecrolimus) also reduce itching in inflammatory skin conditions. Mirtazapine is effective for the itching associated with malignancies. Nursing care for the skin can include oatmeal soap or baths, coolants (topical menthol), and warm compresses for comfort. The use of alkaline soaps and environmental triggers, such as overheating, should be avoided.

VA Palliative Care Services

For patients in the VA system, palliative care is part of the VA Standard Medical Benefits Package; all enrolled Veterans are eligible if they meet the clinical need for the service. In the VA palliative care program, the focus is on improving quality of life, relief of suffering, and control of symptoms so patients can carry out day-to-day activities and focus on what is most important to them. VA palliative care can be combined with active treatment of the underlying disease process. Details specific to VA patients can be found on the Department of Veterans Affairs website, https://www.va.gov/GERIATRICS/Guide/LongTermCare/Palliative_Care.asp#. A helpful description of palliative care for patients is

available there, including details on available services, a shared decision making worksheet, and a link to help locate resources and services locally.



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KEY POINTS

- A Women Veterans Program Manager is available at every VA Medical Center to assist in providing care for women Veterans.
- Nearly one quarter of people living with HIV in the United States are women.
- In the United States, women infected with HIV are less likely than men infected with HIV to receive ARV.
- General preventive strategies and health maintenance are all part of routine care for women infected with HIV.
- Women should receive reproductive counseling.
- For pregnant women and women who may become pregnant, avoid starting an EFV-based regimen.
- Women with HIV have increased risk of developing abnormal cervical, vaginal, vulvar, and anal cytology, with possible progression to squamous carcinoma, especially if the CD4 count is <200 cells/ μ L.
- Women with HIV have higher rates of persistence and recurrence of herpes simplex virus, human papillomavirus (HPV), bacterial vaginosis, and candidal genital tract infections compared with their counterparts uninfected with HIV.
- Women with HIV are at increased risk of neuropsychiatric disease and should be screened accordingly.
- All women Veterans, including those with HIV, should be screened for military sexual trauma and exposure to intimate partner violence.
- All women Veterans, including those with HIV, should be screened for breast cancer and osteoporosis at age appropriate times.



BACKGROUND

Epidemiology

In the United States, according to 2015 CDC data:

- Nearly one quarter of people living with HIV are women.
- Heterosexual transmission is the main mode of HIV acquisition among women (86% in 2015), followed by injection drug use.
- Rates of HIV infection have declined by 20% from 2010-2014.
- African American women are disproportionately infected with HIV.
 - In 2015, the diagnosis rate of both HIV/AIDS and AIDS was 61% in African American women.
- Hispanic/Latina women made up 15% of the HIV diagnosed population while 19% were White.

Note: Some medications mentioned in this chapter may not be available on the VHA National Formulary (<https://www.pbm.va.gov/NationalFormulary.asp>). Consult VA pharmacists for alternatives.

- Women infected with HIV are less likely than their male counterparts to be on ARV therapy, largely because of decreased access to health care and competing priorities.

Natural History

- Women generally have lower viral loads than men at the time of seroconversion.
- On average, HIV RNA levels are at least 50% lower in women than in men with the same CD4 cell counts and duration of HIV infection.
- From seroconversion, the time to the development of AIDS and overall mortality are the same for women and men, despite the difference in HIV RNA levels.
- Virologic and CD4 responses to ARV therapy are the same for women and men.

Risks for Women with HIV

- Women tend to be diagnosed later in the course of HIV than men, which leads to later access to care, and a more advanced disease state.
- Barriers to care include:
 - Child and/or family care obligations, transportation limitations, lack of insurance, fear of disclosure (particularly to male partners, community and social networks), denial, and cultural mistrust of the health care system
 - Perception of their own need for medical care as being of low priority
- Depression: A prospective cohort study showed women who self-reported chronic depressive symptoms were twice as likely to have CD4 decline and more likely to die than women with mild or no depressive symptoms.

Pharmacologic Considerations for Women with HIV

- Limited pharmacokinetic studies show differences in ARV metabolism between women and men.
- Variation may exist due to differences in body weight plasma volume, gastric emptying time, plasma protein levels, cytochrome P (CYP) 450 activity, drug transporter function, and excretion activity.
- Women often have higher serum drug levels of certain ARVs, including EFV, NVP, IDV, LPV/r, and SQV/r.
- EVG/COBI/FTC/TAF (Genvoya) is used to treat adults and children >77lbs, >12 years of age who have never experienced ARV therapy; or to replace other HIV medication regimens when:

- the viral load is less than 50 copies/mL, and
- the same HIV regimen has been in place for at least six months, and
- there has been no treatment failure, and
- no drug resistance mutations to EVG/COBI/FTC/TAF, or
- no recent use of nephrotoxic agents.
- EVG/COBI/FTC/TAF is not recommended in patients with severe renal impairment (estimated creatinine clearance below 30mL per minute).
- Women are less likely to have decreases in limb fat but more significant decreases in bone mineral density.
 - Higher risk for osteopenia, osteoporosis, and fractures – especially after menopause. This risk is exacerbated with the additions of ARVs.
 - TDF and PI-based regimens are associated with more bone loss than other NRTIs or RAL.
 - Consider using ABC or TAF in patients who are at risk for osteopenia or osteoporosis.
 - Information regarding dosage adjustment of ARVs for women (pregnant or nonpregnant) is lacking.
 - Metabolism of ARVs may be altered during pregnancy; particularly in the third trimester.
 - Consult the Perinatal Guidelines for the treatment of pregnant women with HIV.
- Some ARVs should not be used by pregnant women or those who may become pregnant, because of potential teratogenicity or other toxicity.
 - Regarding EFV-based therapy, neural tube defects have been reported; however, current recommendations are to keep the mother on current ARVs if she becomes pregnant.
 - Consider avoiding EFV-based regimens in women of child-bearing age, particularly in light of other available options, such as RAL, currently recommended for use during pregnancy.
- Some ARVs have significant interactions with certain hormonal contraceptives thus ARVs and contraceptives should be selected with this in mind. See **Potential ARV Interactions**, below.

Health maintenance: With prolonged survival in the era of ARV therapy, preventive strategies and health maintenance measures such as control of hypertension, smoking cessation, minimizing cardiovascular risk factors, and routine screening for osteoporosis and cancer (cervical, breast, and colon) are all part of routine care for women infected with HIV. See **Evaluation and Management**, below, as well as **Hypertension** (p. 479), **Dyslipidemia** (p. 417), and **Tobacco Use** (p. 127) for further information on these topics.

This chapter will address these commonly encountered issues for women infected with HIV:

- Reproductive and hormonal issues
- Interactions of ARVs with hormonal contraceptives
- Screening for neuropsychiatric disorders
- Screening for military sexual trauma and domestic violence
- Screening for cancer(s), osteoporosis, and STD
- Cervical dysplasia
- Osteoporosis
- Genital tract infections



EVALUATION AND MANAGEMENT

Note: A Women Veterans Program Manager is available at every VA Medical Center to assist in providing care for women Veterans, including those with HIV infection.

HIV Prevention See also **Prevention of HIV Transmission with Positives**, p. 45.

	Recommendations	Comments
Prevention of HIV transmission	<ul style="list-style-type: none"> • Evaluate each patient's need for HIV prevention strategies on a regular basis. • Evaluate patient for high-risk behaviors (e.g., alcohol misuse, substance use disorders) that may predispose to high-risk behaviors. • Encourage use of condoms (male or female) during all sexual encounters. <ul style="list-style-type: none"> • Other barriers: diaphragm, cervical cap limited have little efficacy in preventing HIV transmission. • Screen regularly for STDs, and treat as needed. • Use of nonoxynol-9 is not recommended due to increased risk of HIV transmission as it may result in vaginal irritation and lacks the ability to prevent STDs. 	<ul style="list-style-type: none"> • If used correctly and consistently, condoms are effective for reducing risk of transmission of HIV and other STDs, including HPV. • Condoms may also be effective for contraception, but only if used optimally (see below). • Abstinence is effective for preventing HIV, other STDs, and pregnancy. • PrEP • In some women, HIV viral load may be substantially higher in vaginal secretions than in blood; thus risk of sexual transmission of HIV may not be predicted by plasma viral load. • Tenofovir gel, dapivirine ring, and implantable devices are not yet available.

	Recommendations	Comments
-	<ul style="list-style-type: none"> • ARV therapy has been shown to reduce risk of HIV transmission to uninfected partners. • Preexposure prophylaxis (PrEP): Two studies have shown efficacy and safety of daily oral TDF/FTC (as part of a comprehensive prevention strategy) in both women and men in heterosexual serodiscordant relationships. One study showed efficacy of daily oral TDF alone, however, this is not currently recommended. FEM-PrEP and VOICE did not show efficacy of oral PrEP in women due to low adherence. • Tenofovir 1% vaginal gel has been shown to be effective but subsequent studies were not consistent with this due to low adherence rates. • Dapivirine impregnated intravaginal rings have been shown to be effective. • Additional studies are underway to evaluate the safety and efficacy of implantable ARV-impregnated devices for prevention. 	<ul style="list-style-type: none"> • Further studies are evaluating the combination of hormonal contraception plus ARV therapy.

Reproductive and Hormonal Issues

Issue	Recommendations	Comments
Contraception	<ul style="list-style-type: none"> • Condoms (male or female) during all sexual encounters may lead to high failure rates if used suboptimally; thus it is wise to consider adding a second contraceptive method. If used correctly and consistently condoms are also effective in the prevention of HIV transmission. 	<ul style="list-style-type: none"> • 50% of pregnancies in the United States are unplanned. • On a regular basis evaluate each woman's pregnancy intent and need for contraceptive information and methods.

Issue	Recommendations	Comments
	<ul style="list-style-type: none"> • Intrauterine devices (IUDs), particularly the Mirena levonorgestrel-releasing (LNG) device, and the copper-T devices have been shown to be safe for use by women infected with HIV and do not increase HIV viral shedding. Apparent decrease of HIV target cell populations in the genital tract may prevent ascending infections of other STIs. • Other barriers: diaphragm, cervical cap • Spermicides (e.g., non-oxynol-9) are not recommended due to the increased risk of HIV transmission resulting from vaginal irritation. • Oral hormonal contraceptives: Note drug-drug interactions with some ARVs. See Potential ARV Interactions, below. • Injectable contraceptives (medroxyprogesterone [DMPA, Depo-Provera]): appear to be effective for women on ARVs. (However, see Potential ARV Interactions, below.) • Transdermal/patch and intravaginal ring (Nuvaring): little information on interactions with ARVs but likely similar to those of oral hormonal contraceptives. See Potential ARV Interactions, below. 	<ul style="list-style-type: none"> • For women who intend, or desire pregnancy, provide preconception counseling. See below. • Avoid use of EFV with women using inadequate or inconsistent contraception due to the risk of teratogenicity in the first trimester. • Interactions between oral hormonal agents and many ARVs may decrease contraceptive efficacy. See Potential ARV Interactions, below. Less data exists for drug-drug interactions with other formulations. • Possible adverse effects of hormonal contraceptives include thrombosis, myocardial infarction (estrogen/progesterone), stroke, menstrual irregularities, breast tenderness, weight gain, mood changes, loss of bone mineral density (DMPA), increased risk of breast cancer and smoking increases risk of thromboembolic events. • DMPA: Conflicting data has increased in regards to the possible increased risk of HIV transmission between a woman infected with HIV to a male partner or acquisition by uninfected woman from a male infected with HIV for women on DMPA. As an aside, study participants were not on ARV therapy nor did the study meet the necessary power to be reliable.

Issue	Recommendations	Comments
-	-	<ul style="list-style-type: none"> • A pool of 10 studies showed DMPA increased risk of HIV acquisition but not when combined with oral contraceptives (COC). • Adjusted analysis from 18 studies showed increased risk of HIV acquisition with DMPA when not used with COC. • For women in whom hormonal methods are contraindicated (e.g., history of thrombosis, thrombophilia, or cancer) the copper-T IUD may be safe and effective.
Preconception	<p>Preconception counseling is needed for all women who intend to become, or who may, become pregnant. Preconception counseling and care includes:</p> <ul style="list-style-type: none"> • Education regarding HIV and pregnancy, risk of transmission to fetus or uninfected partners, and available measures to reduce risk. • Initiation of folate supplementation (higher dosage is required for women who take TP-SMX.) See Pregnancy, below. • Screening tests: rubella titers, varicella titers in patients with no varicella history, HBV serologies, HCV antibody, Toxoplasma immunoglobulin G, cytomegalovirus, tuberculosis screening (purified protein derivative or Quantiferon), complete blood count and consider fasting glucose. 	<ul style="list-style-type: none"> • Many women infected with HIV become pregnant; intentionally or unintentionally. It is important to discuss each patient's intentions and desire to bear children at entry to care and periodically thereafter. • Women with HIV infection have been noted to have increased rates of infertility compared to women not infected with HIV. • Tubal infertility is more common among with with HIV. • For women with difficulty conceiving, referral for evaluation of possible etiologies for infertility to include evaluation of endocrine, uterine, tubal, and male factors, should occur in advance of referral for assisted reproduction. • Screen and treat both patients for STDs.

Issue	Recommendations	Comments
-	<ul style="list-style-type: none"> • Vaccinations as appropriate. • PAP smear, STD screening (gonorrhea, chlamydia, syphilis, trichomoniasis). • Nutrition evaluation. • Substance abuse and mental health screening and treatment as indicated. • Referral to reproductive health specialist with experience in working with women infected with HIV. See Pregnancy, below. • Referral for prenatal genetic counseling. <p>Assist women to become pregnant in ways that have lowest risk of HIV infection for partner (if HIV uninfected) and for fetus.</p> <p>Note: VA does provide in vitro fertilization or other assisted reproduction services for service-connected infertility. VA now covers Infertility Services through the Choice Program. However, the infertility has to be connected to their service-connect disability. So HIV itself is not enough justification for IVF.</p> <ul style="list-style-type: none"> • For an woman uninfected with HIV with a male partner infected with HIV, consider sperm washing, in vitro fertilization (IVF), intracytoplasmic sperm injection (ICSI), preexposure prophylaxis, ARV therapy with virologic suppression for the infected partner. Full disclosure of genetic and other risks of assisted reproduction are paramount. 	<ul style="list-style-type: none"> • Utilize ARVs to maximally suppress the infected partner. • Use PrEP for prevention of HIV in uninfected partner. • Male circumcision.

Issue	Recommendations	Comments
-	<ul style="list-style-type: none"> • Sperm washing results in sperm that is reported to be >99.9% free of HIV virus. • Note: Legal issues in some states may limit access to reproductive services. • Maximize ARV therapy efficacy, selecting ARVs appropriate for use during pregnancy. See below. • Avoid potential teratogens, including EFV, ribavirin, hydroxyurea, thalidomide, and some antiepileptic drugs. • Optimize control of other medical conditions (e.g., hypertension, diabetes). 	-
Pregnancy	<ul style="list-style-type: none"> • Detailed information on care of pregnant patients infected with HIV is available at www.hiv.gov. • Refer to an obstetrician who has expertise working with women infected with HIV. For centers that do not have such expertise available, consultation is available through the National Perinatal HIV Consultation and Referral Service, http://www.ucsf.edu; the hotline is 888-448-8765). • For pregnant women or women who may become pregnant, give 0.8 mg folate daily (folate dosage should be 4-5 mg QD for women who take TMP-SMX, to overcome the folate-antagonist effects of TMP-SMX). 	<ul style="list-style-type: none"> • Goals include maximal suppression of HIV RNA to prevent HIV transmission and to optimize the patient's health. • Higher risk of perinatal transmission with: <ul style="list-style-type: none"> • High viral load • Low CD4 count • Advanced HIV infection • Poor nutrition • Drug use • STD • Vaginal delivery (if HIV RNA >1,000 copies/mL) • Invasive monitoring • Prolonged rupture of membranes • Chorioamnionitis • Without ARV therapy the risk of transmission is 25%, with PI-based ARV therapy the risk of transmission is 1% in the United States.

Issue	Recommendations	Comments
-	<ul style="list-style-type: none"> • ARV therapy during pregnancy: • Test for HIV resistance before initiating ARV therapy. • Continue or give combination ARV therapy with goal of maximal virologic suppression. • Recommended agents for use during pregnancy*: <ul style="list-style-type: none"> • ABC/3TC, TDF/FTC, or TDF/3TC in combination with ATV/r, DRV/r, or RAL. • Alternative ARVs during pregnancy: <ul style="list-style-type: none"> • NRTIs: AZT/3TC • NNRTIs: EFV or RPV • PIs: LPV/r • Insufficient data: COBI, DTG, EVG/c/TDF/FTC, MVC, TAF-containing regimens: Avoid use of EFV, in the first trimester due to the risk of teratogenicity. Pregnant women taking EFV as part of an effective ARV therapy regimen at the time they present for antenatal care may continue EFV. • If possible, screen for HLA-B*5701 before treatment with ABC to potentially reduce the risk of HSR 	<ul style="list-style-type: none"> • Pharmacokinetic changes during pregnancy may alter serum levels of some ARVs, check USPHSTF guidelines for recommended dosage adjustments, and consult with a pharmacologist. • Many experts recommend increase in LPV/r dosage to 600/150 mg BID during 3rd trimester. • DRV/r should be dosed 600/100 mg BI. • Ongoing study evaluating DTG PK in pregnancy but preliminary data suggest lower levels in the third trimester → strict adherence is necessary if used. • RAL is recommended for use. • Some evidence suggest ARV therapy may increase rates of preeclampsia. • Consider scheduled cesarean section delivery if HIV viral load is >1,000 copies/mL near time of delivery. • Do not delay initiation of ARVs pending genotype results – adjust as needed when results return. • Report cases of prenatal exposure to the Antiretroviral Pregnancy Registry, http://www.apregistry.com/. • Continue maternal ARVs before, during, and after delivery.
Breast-feeding	<ul style="list-style-type: none"> • Breast-feeding is not recommended in the United States to avoid the risk of HIV transmission through breast milk. 	-

Issue	Recommendations	Comments
<p>Menstrual irregularities and menopause</p>	<ul style="list-style-type: none"> • Evaluate menstrual irregularities as in women not infected with HIV. Initial considerations include: <ul style="list-style-type: none"> • For abnormal bleeding, determine source of bleeding (bladder, urethra, vagina, uterus), with further evaluation depending on source. • Pregnancy test. • Consider polycystic ovarian syndrome (PCOS) in women with amenorrhea or hypomenorrhea and features suggestive of PCOS (clinical or serum hyperandrogenism, glucose intolerance, obesity). • Consider menopause: Evaluate with follicle-stimulating hormone (FSH) to confirm. • Consider checking FSH and prolactin for secondary causes of amenorrhea. • Consider hypothyroidism (check TSH). • For intermenstrual bleeding, evaluate for estrogen or progestin breakthrough on hormonal contraceptives, complications of intrauterine device, polyps, genital tract cancers, genital tract infections such as endometritis. • For post coital bleeding, evaluate for cervical malignancies and lesions and STDs. 	<ul style="list-style-type: none"> • Women infected with HIV more commonly experience irregular cycles and amenorrhea but it is not entirely clear whether this is associated with HIV infection itself. Some research suggests an association between CD4 count and ovulatory status. • Confounders include weight loss, psychiatric medications, hormonal treatments, substance abuse, stress, and chronic disease. • Prolonged amenorrhea, without ovarian failure in women infected with HIV is associated with low body mass index and low serum albumin. • Combined analysis of data from the HERS and WHIS cohorts showed women on ARV therapy had good CD4 response and lower rates of menstrual irregularities than women uninfected with HIV. • In the WHIS study, the average age at onset of menopause was 48, for both women infected and uninfected with HIV of similar demographics. • There is a blunted CD4 recovery to ARV therapy among postmenopausal women with HIV. This is postulated to be related to lower levels of estrogen and with decrease in thymic volume that is associated with aging.

Issue	Recommendations	Comments
-	<ul style="list-style-type: none"> Treatment of menopausal symptoms may include the addition of hormonal therapy just as in the woman uninfected with HIV. Keep in mind, potential adverse effects, as well as drug-drug interactions exist between estrogens and some ARVs. See Potential ARV Interactions, below. 	-
Sexual function	<p>Evaluate a woman's perceived level of satisfaction of her sexual function, especially factors related to perceptions, of suboptimal sexual function such as:</p> <ul style="list-style-type: none"> Physical, sexual, emotional abuse Relational problems Depression STDs Medications Pelvic pain Constitutional symptoms Peripheral and autonomic neuropathy Hypogonadism Other medical and psychiatric comorbidities 	<p>Sexual function in women infected with HIV is a neglected area of study. Discuss patient's concerns candidly.</p> <ul style="list-style-type: none"> Patient-reported sexual dysfunction is associated with nonadherence to ARV Therapy Sexual dysfunction may be a marker for depression, worsening health status including pain syndromes, or intimate partner violence. A wide variety of medications, especially psychiatric, antiepileptic, and cardiovascular drugs, are associated with sexual dysfunction.

Abbreviations: HERS = Heart and Estrogen/Progestin Replacement Study; USPHSTF = U.S. Public Health Services Task Force; WIHS = Women's Interagency HIV Study

*Public Health Service Task Force Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States; May 24, 2010.

For Couples Who Want to Conceive When One or Both Partners are Living with HIV:

Expert consultation is recommended so that approaches can be tailored to couples' specific needs (AIII).

Partners should be screened and treated for genital tract infections before attempting to conceive (AII).

Partners living with HIV infection should attain maximum viral suppression before attempting conception to prevent HIV sexual transmission (AI) and, for women living with HIV, to minimize the risk of HIV transmission to the infant (AII).

For couples with differing HIV status. When the woman is living with HIV, assisted insemination at home or in a provider's office with a partner's semen during the peri-ovulatory period is recommended as a conception strategy that eliminates the risk of HIV transmission to the partner without HIV (AIII).

For couples with differing HIV status. When the man is living with HIV, the use of donor sperm from a man who is HIV-uninfected can be used as a conception strategy that eliminates the risk of HIV transmission to the partner without HIV (BIII).

For couples with differing HIV status. When the partner living with HIV is on ARV therapy and has achieved sustained viral suppression, sexual intercourse without a condom limited to the 2 to 3 days before and the day of ovulation (peak fertility) is an approach to conception with very low risk of sexual HIV transmission to the partner without HIV (BII).

For couples with differing HIV status who attempt conception via sexual intercourse without a condom (despite counseling) when the partner living with HIV has not been able to achieve viral suppression or when the viral suppression status is not known, administration of antiretroviral pre-exposure prophylaxis (PrEP) to the partner without HIV is recommended to reduce the risk of sexual transmission of HIV (AI). Couples should still be counseled to limit sex (without condoms) to the period of peak fertility (AIII).

For couples with differing HIV status who attempt conception (sexual intercourse without a condom limited to peak fertility) when the partner living with HIV has achieved viral suppression, it is unclear whether administering PrEP to the partner without HIV further reduces the risk of sexual transmission (CIII).

See also **Pregnancy and HIV-Limiting Transmission to Fetus**, p. 71.

<https://aidsinfo.nih.gov/guidelines/html/3/perinatal/153/reproductive-options-for-couples-with-the-same-or-differing-hiv-status>

Evidence Rating:

Strength of Recommendation:

- A: Strong recommendation for the statement
- B: Moderate recommendation for the statement
- C: Optional recommendation for the statement

Quality of Evidence for the Recommendation:

- I: One or more randomized trials with clinical outcomes and/or validated laboratory endpoints
- II: One or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes
- III: Expert opinion

! POTENTIAL ARV INTERACTIONS

Hormonal Contraception and ARVs

Drug interactions between oral contraceptive agents and many PIs and NNRTIs may affect the serum levels of either the hormonal agent or the ARV. In some cases, contraceptive efficacy, or the potential for side effects may be significantly affected. Dosage adjustments may be required and some combinations are contraindicated. See **Table** below for details.

There is negligible data on potential interactions between ARVs and non-oral hormonal contraceptives. Transdermal (patch) and transvaginal (intra-vaginal ring) contraceptive devices contain ethinyl estradiol (EE); thus caution should be used on a theoretical basis with ARVs that increase the serum estradiol levels. DMPA (Depo-Provera) is a progestin, therefore interactions with ARVs may mirror those of norethindrone (NE). This may be cause for concern if DMPA is used with ARVs that increase NE levels, because DMPA is long-acting and has sustained serum levels. Implantable progestin-only contraceptives have reduced efficacy with EFV and increased exposure with LPV/r. Intrauterine levonorgestrel devices appear to maintain efficacy although robust data are lacking.

There are no significant known interactions between hormonal contraceptives and NRTIs, integrase inhibitors, with the exception of EVG/c, or CCR5 antagonists.

Potential Interactions between Oral Contraceptives and PIs NNRTIs, or INSTIs

Decreased EE or NE levels

PIs: <ul style="list-style-type: none">• ATV/r• DRV/r• LPV/r• RTV	Risk of contraceptive failure; use alternative (or additional) contraceptive method. (Oral contraceptive may be used with ATV/r, but it should contain ≥ 30 mcg of EE). Only commonly used first line/alternative agents are included in this review.
NNRTIs: <ul style="list-style-type: none">• NVP• EFV	Risk of contraceptive failure; use alternative (or additional) contraceptive method. EFV significantly reduced exposure to levonorgestrel for emergency contraception.
INSTIs: <ul style="list-style-type: none">• EVG/c	Significant reduction in EE exposure. Risk of contraceptive failure; use alternative or additional contraceptive method.

Increased EE or NE levels

<p>PIs (without RTV):</p> <ul style="list-style-type: none"> • ATV 	<p>ATV: Carries the risk of EE or NE adverse effects (e.g., deep vein thrombosis). Use alternative method of contraception or lowest effective dosage with careful monitoring for adverse effects. If given concurrently oral contraceptive should contain ≥ 30 mcg of EE; however, doses < 25 mcg have not been studied.</p>
Mixed effects	
<p>NNRTIs:</p> <ul style="list-style-type: none"> • ETR 	<p>\uparrow EE, \downarrow NE; no dosage adjustment.</p>

Neuropsychiatric Disorders

Recommendations	Comments
<p>Screen for neuropsychiatric disorders in women infected with HIV.</p> <ul style="list-style-type: none"> • Depression • Dementia • Posttraumatic stress disorder (PTSD) • Personality disorders <p>Perform neuropsychiatric testing as needed.</p>	<p>Neuropsychiatric disorders are common in individuals infected with HIV:</p> <ul style="list-style-type: none"> • Direct effects of HIV on neuronal function • Underlying psychiatric disease • Affective disorders • Prior trauma • Social comorbidities <p>Women with HIV are at increased risk of HIV-associated psychiatric disease, especially HIV-related dementia, but also at risk of under diagnosis and under treatment of depression. Neuropsychiatric testing is recommended to establish diagnosis and provide a baseline of cognitive function.</p> <p>Owing to increased rates of depression and PTSD in women Veterans aggressive screening and treatment of depression in women infected with HIV is recommended. According to one prospective longitudinal cohort study, women with chronic depression and HIV, are twice as likely to die compared to those with mild or no depressive symptoms. Substance abuse is often comorbid with PTSD and depression.</p> <p>For women with HIV infection, especially those with multiple responsibilities, psychosocial needs may be complex requiring multidisciplinary team care. Research</p>

Recommendations	Comments
-	<p>suggests that case management can improve outcomes, transdisciplinary care, and treatment adherence.</p> <p>For further information, see Depression, p. 149.</p>

Military Sexual Trauma and Domestic Violence (Intimate Partner Violence)

<p>Military sexual trauma (MST)</p>	<ul style="list-style-type: none"> • Screen all Veterans, including female Veterans, for MST. • Refer Veterans with MST to the designated MST Counselor or team; referral to a local Vet Center may be an appropriate alternative based on available services. 	<ul style="list-style-type: none"> • MST is common in women Veterans and likely underreported. MST-related PTSD is associated with a variety of medical and psychiatric problems including chronic pelvic pain, GI problems, chronic pain, substance abuse and mood disorders.
<p>Domestic violence</p>	<ul style="list-style-type: none"> • Consider screening with the E-HITS scale: <ul style="list-style-type: none"> • Hurt: Has your partner ever physically hurt you in the past 12 months? • Insult: Has your partner ever insulted you in the past 12 months? • Threaten: Has your partner ever threatened to harm you in the past 12 months? • Scream: Has your partner ever screamed or cursed at you in the past 12 months? • Extended: Has your partner ever forced you to have sexual activities in the past 12 months? 	<ul style="list-style-type: none"> • Domestic violence is prevalent among both female Veterans and women living with HIV infection. • Screening instruments such as the E-HITS scale have been validated. • There is weak evidence for the efficacy of interventions in the health care setting.

Issue	Recommendations	Comments
	<p>Each question is answered on a 5-point scale: 1 = never; 2 = rarely; 3 = sometimes; 4 = fairly often; 5 = frequently. The score ranges from 4 to a maximum of 25. A score of ≥ 10 is considered diagnostic of abuse.</p> <ul style="list-style-type: none"> • Look for evidence of physical abuse such as bruises, fractures, and other injuries accompanied by implausible explanation(s) of such injuries. • If abuse is documented or suspected: <ul style="list-style-type: none"> • Refer to the Intimate Partner Violence Coordinator who will coordinate care for the Veteran. • Consult Social Work Service. • Refer the patient to community domestic violence agencies. • Work with the patient to develop an emergency safety plan 	

Screening: Cancer, Osteoporosis, and STDs

Note: For other routine **cancer screening**, see **Cancer Screening**, p. 201.

Test	Recommendations	Comments
<p>Cervical cancer screening:</p> <ul style="list-style-type: none"> • Cervical PAP test (smear or liquid cytology) 	<p>Women infected with HIV Aged <30 years:</p> <ul style="list-style-type: none"> • Document date of diagnosis. • If normal, repeat in 6 to 12 months. 	<ul style="list-style-type: none"> • Women infected with HIV are more likely than women uninfected with HIV to be infected with HPV especially with oncogenic HPV types.

Test	Recommendations	Comments
-	<ul style="list-style-type: none"> • If both PAP results are normal, repeat annually until three consecutive normal PAP Tests then f/u tests every 3 years. • Co-testing is not recommended. <p>Women Infected with HIV ≥30 years:</p> <ul style="list-style-type: none"> • Cervical cancer screening should be lifelong (i.e. should not end at 65 years of age). • Either PAP testing only or co-testing (with HPV) are acceptable. • PAP testing only: <ul style="list-style-type: none"> • Time of diagnosis • Repeat in 6-12 months • Three consecutive tests → every 3 years • PAP and HPV co-testing <ul style="list-style-type: none"> • Time of diagnosis or at age 30 • If negative, can repeat in 3 years. • If PAP normal and HPV positive, repeat co-testing in one year and if either are abnormal, referral to colposcopy. • If HPV 16 or 16/18 identified, referral to colposcopy. 	<ul style="list-style-type: none"> • Dysplasia may involve the cervix, vulva, vagina, or anus. • Abnormalities on cervical colposcopy are seen in 64% of women with CD4 counts of <200 cells/μL and 34% of those with CD4 counts of >400 cells/μL, therefore, CD4 counts are not a reliable indicator of risk of HPV-related dysplasia. • Women infected with HIV have decreased rates of clearance of HPV; as a result they have an increased risk of disease progression and recurrence. • For management of abnormal results, see Cervical Dysplasia and Management of Abnormal PAP Smear Result, below. • Consider HPV vaccine if age <26 years.
<p>Vulvar and vaginal cancer screening:</p> <ul style="list-style-type: none"> • Visual and manual inspection 	<ul style="list-style-type: none"> • Routine screening for vulvar or vaginal cancer is not recommended unless there is a h/o high-grade CIN, adenocarcinoma in situ, or invasive cervical cancer. • Evaluate at time of cervical PAP test a vaginal cuff PAP test. 	<ul style="list-style-type: none"> • Women infected with HIV have elevated rates of vulvar and vaginal neoplasia. • Lesions may be multifocal, extensive, and recurrent, and possibly have an unusual appearance, sometimes progressing rapidly, especially in women with CD4 counts

Test	Recommendations	Comments
-	<ul style="list-style-type: none"> Suspicious lesions: colposcopy; biopsy. <p>If abnormal vaginal cuff PAP test, with no visible vaginal colposcopic abnormalities, → Lugol's iodine for vaginal staining is recommended.</p>	<p>of <200 cells/μL</p> <ul style="list-style-type: none"> Apparent condylomata that are resistant to treatment and, any unusual cervical or vulvar lesions, should be referred for biopsy. Evaluate RPR.
<p>Anal cancer screening:</p> <ul style="list-style-type: none"> Digital rectal examination (DRE) Anal PAP test 	<ul style="list-style-type: none"> No national guidelines for anal cancer screening are available but it is important to consider baseline evaluation: <ul style="list-style-type: none"> Annual DRE and anal PAP screening if patient practices receptive anal sex if and baseline result was normal. Use polyester swab and liquid cytology-method if available. 	<ul style="list-style-type: none"> Anal dysplasia and anal cancer rates among women infected with HIV are not fully known but appear to be higher than those for women uninfected with HIV. Anal dysplasia is seen in women with and without a history of receptive anal sex. ARV therapy has not been shown to prevent or alter the course of anal dysplasia. ASCUS, LSIL, HSIL: Refer for high-resolution anoscopy with biopsy. Some studies indicate cost-effectiveness with screening for lesions using anal cytology and treating precancerous lesions to reduce risk of anal cancer while providing clinical benefits comparable to prevention of other OIs. See Anal Dysplasia, p. 315.
<p>Breast cancer screening:</p> <ul style="list-style-type: none"> Mammogram 	<ul style="list-style-type: none"> For women at average risk American Cancer Society recommends: <ul style="list-style-type: none"> Age 40-44: conversation with patient Age 45-55: annual mammogram 	<ul style="list-style-type: none"> Women infected with HIV do not appear to have elevated risk of breast cancer.

Test	Recommendations	Comments
-	<ul style="list-style-type: none"> Age ≥55: mammogram every other year 	-
<p>Osteoporosis/osteopenia screening:</p> <ul style="list-style-type: none"> Dual-energy X-ray absorptiometry (DEXA) bone densitometry 	<ul style="list-style-type: none"> DEXA screening for women with HIV is >50. Also consider for thin female smokers >40 years of age. Every 2 years for patients with osteoporosis who are treated with bisphosphonates. 	<ul style="list-style-type: none"> Age and previous fracture are the most significant risk factors. See Osteoporosis, below, for more information and treatment recommendations.
<p>STD testing:</p> <ul style="list-style-type: none"> RPR, VDRL Cervical GC and CT (NAAT or culture of first-void urine or cervical specimen) Rectal or pharyngeal testing for GC and CT, based on possible risks or exposures (NAAT, if available, or culture for GC) Trichomonas (wet-mount examination or culture of vaginal secretions) HBV, HCV screening 	<ul style="list-style-type: none"> Conduct STD risk assessment at each visit – Five P's: Partners, Practices, Prevention of Pregnancy, Protection from STDs, and Past History of STDs. Perform testing baseline, repeat according to risk or exposure; e.g., every 3-6 months for women with new sex partners since previous examination. Counsel on STD prevention. Pre-exposure vaccination with HPV vaccine – recommended through age 26 for all females. HBV series if not received or does not have immunity. 	<ul style="list-style-type: none"> STDs should be treated to prevent health complications for the patient, as well as prevent perinatal transmission or transmission to sex partners. Inflammatory STDs may increase risk of HIV transmission to uninfected sex partners. See Prevention of HIV Transmission with Positives, p. 45. HCV screening recommended annually if risk for acquisition is present.

Abbreviations: ASCUS = atypical squamous cells of undetermined significance; CT = Chlamydia trachomatis; GC = Neisseria gonorrhoea; HSIL = high-grade squamous intraepithelial lesion; LSIL = low grade squamous intraepithelial lesion; NAAT = nucleic acid amplification test; ACOG = American College of Obstetricians and Gynecologists; USPSTF = U.S. Preventive Services Task Force; ACP = American College of Physicians

Cervical Dysplasia and Management of Abnormal PAP Smear Results

Epidemiology and Diagnosis	Management and Treatment
<ul style="list-style-type: none"> • HPV prevalence is higher among women infected with HIV than among women uninfected with HIV. • In the WIHS cohort, women living with HIV had higher cervical cancer incidence that was more pronounced in the severely immunosuppressed woman. • 2-5 fold higher incidence of invasive cervical cancer with increasing rates in women with lower CD4 counts. • Meta-analysis of HPV types in women living with HIV indicated: 36% any HPV and 12% multiple types of HPV. • Women infected with HIV who have increased persistence of HPV, with history of abnormal PAPs, are two to eight times more likely to develop cervical cancer. • Persistence of HPV is related to more cases of abnormal cervical cytology. • Women with low CD4 counts tend to harbor high-risk HPV types. • The time between diagnosis of carcinoma in situ and development of invasive disease is shorter among women infected with HIV who are not on ART than among women uninfected with HIV; 3.2 vs. 15.7 years. • However, ARV therapy has not been shown to consistently prevent or alter the course of cervical dysplasia in women infected with HIV. <p>See Screening: Cancer, Osteoporosis, and STDs, above, for screening recommendations.</p>	<ul style="list-style-type: none"> • Most experts recommend more aggressive management of women infected with HIV than women uninfected with HIV. • The American Society for Colposcopy and Cervical Pathology (ASCCP) recommends managing women infected with HIV no differently than women uninfected with HIV. • Address other risk factors for cervical cancer: <ul style="list-style-type: none"> • Smoking • Chlamydial infection • Obesity • Long-term oral contraceptive use • Family history • Poverty • ≥3 full-term pregnancies • Diet poor in fruits and vegetables • Abnormal result <30 years and ≥30 years <ul style="list-style-type: none"> • ASC-US PAP: if reflex HPV positive → colposcopy. • If HPV testing not available → repeat cytology in 6-12 months. If result ≥ASCUS on repeat cytology, refer to colposcopy. • ASC-H (atypical squamous cells, cannot exclude HSIL), LSIL, HSIL, and atypical glandular cells: Refer all patients with these findings for colposcopy. Note that some laboratories use the cervical intraepithelial neoplasia (CIN) 1, 2, 3 classification and these patients should also be referred for colposcopy.

Epidemiology and Diagnosis

Background

- In small cohort studies women infected with HIV had twice the rate of osteopenia (by DEXA) as women uninfected with HIV matched for age, race, and BMI.
- Fracture rates are higher in HIV-infected patient populations.
- HIV infection itself appears to be independently associated with reduced bone mineral density.
- Exposure to ARVs is associated with a 2-6% decrease in BMD in the first 2 years of treatment.
- TDF appears to cause greater initial decrease in BMD compared with other ARVs.
- EFV-based regimens have been associated with lower Vitamins D levels mixed reports with PIs.

Risk factors

- History of fracture as an adult
- Advanced age
- Female sex
- Race (Asians and Caucasians at higher risk)
- Family history
- Low BMI
- Estrogen deficiency at early age (amenorrhea >1 year, early menopause)
- Lifestyle: Current cigarette smoking, alcohol misuse, inadequate physical activity, IVDU
- Poor health/nutrition (e.g., low calcium intake)
- Medications (e.g., corticosteroids, anticonvulsants, proton pump inhibitors, gonadotropin-releasing hormone [GnRH] agonists, lithium)
- Medical conditions: HCV infection, hyperthyroidism, gastrectomy, COPD,

Management and Treatment

Prevention (for all women)

- 25-hydroxy-vitamin D <20 ng/mL: 1,000-2,000 iu calcium to target a level of 30
- Calcium* 1,000 mg per day for premenopausal women; 1,200 mg per day for postmenopausal women, in divided doses
- Exercise: 30 minutes of weight-bearing exercise ≥4 times per week
- Smoking cessation, limited alcohol intake, adequate diet, careful sun exposure
- Women taking calcium and vitamin D supplements in the Women's Health Initiative had a 1% gain in hip bone mineral density and a slight but statistically nonsignificant reduction in hip fracture (hazard ratio: 0.71; 95% confidence interval: 0.52-0.97 [for women with ≥80% adherence]).
- Consider use of TAF or ABC in patients at high risk for osteoporosis.

Treatment

Treat women with:

- Post-menopausal women >50 years with a T-score of the femoral neck or lumbar spine ≤-2.5
- Patients with a history of fragility fracture of the spine or hip
- Patients with low bone mass (T-score -1 to -2.5 at femoral neck or lumbar spine) with and high FRAX score

Treatment options

- Bisphosphonates offer the most clinically significant benefit. Randomized controlled studies show a 56% reduction in hip fractures in patients treated with alendronate. Options include:

Epidemiology and Diagnosis	Management and Treatment
<p>hyperparathyroidism, multiple myeloma, celiac disease, eating disorder, vitamin D deficiency</p> <ul style="list-style-type: none"> • Recurrent falls, dementia <p>Evaluation</p> <ul style="list-style-type: none"> • DEXA screening for women with HIV is >50 years: <ul style="list-style-type: none"> • Normal = T-score above -1 • Osteopenia = T-score between -1 and -2.5 • Osteoporosis = T-score less than -2.5 (fracture-threshold) • FRAX index: Fracture risk assessment tool, developed by the WHO, estimates risk of fracture within 10 years. Available at http://www.shef.ac.uk/. 	<ul style="list-style-type: none"> • Alendronate 70 mg PO once weekly • Zoledronic acid 5 mg IV once yearly <p>Note: There are reports of osteonecrosis of the jaw in patients taking oral bisphosphonates: risk is 1 in 10,000-100,000 patient years and higher in patients with malignancies. Discuss this risk with patients.</p> <p>Plus:</p> <ul style="list-style-type: none"> • Calcium* 1,200 mg per day in divided doses • Vitamin D 800-1,000 IU QD • Smoking cessation • Limited alcohol intake • Exercise: 30 minutes of weight-bearing exercise \geq4 times per week

*Calcium and other divalent cations may lower serum levels of integrase inhibitors; calcium should be taken \geq 2 hours apart from integrase inhibitors.

Genital Tract Infections

Infection	Epidemiology and Diagnosis	Management
<p>HSV</p>	<ul style="list-style-type: none"> • Risk factor for HIV acquisition and transmission. • Of HIV-infected women, 50-90% have concurrent HSV infection. • In the HERS study there was no difference in rates between HIV-infected and high-risk women uninfected with HIV. • Chronic suppressive therapy with acyclovir may increase survival for HIV/HSV-coinfected women who do not take ARVs; this benefit is not demonstrated in patients on ARV therapy. 	<ul style="list-style-type: none"> • Initial episode or severe mucocutaneous outbreak: hospitalize and treat with IV acyclovir (5 mg/kg IV Q8H), changing to PO therapy when lesions improve. Duration of therapy: \geq10 days. • Episodic therapy for outbreaks: acyclovir 400 mg TID, valacyclovir 1,000 mg BID, or famciclovir 500 mg BID for 5-10 days. • Suppressive therapy: Consider for patients with frequent recurrences, especially those with CD4 counts of $<$100 cells/μL, and severe protracted outbreaks: acyclovir 400-800 mg

Infection	Epidemiology and Diagnosis	Management
-	<ul style="list-style-type: none"> • Infection can be primary, non-primary first episode, or recurrent. • Most genital HSV infections occurring in HIV coinfection reflect reactivation syndromes. Symptomatic episodes may be more severe, more frequent, and longer in duration than in HIV-negative women. • Genital HSV in women infected with HIV ranges in appearance from small confined ulcers to painful extensive necrotic lesions accompanied by constitutional symptoms. • Complications seen more commonly in advanced HIV infection include aseptic meningitis, sacral radiculopathy, transverse myelitis, scarring, rectovaginal fistulae. <p>Diagnosis: swab base of lesion for testing via viral culture or HSV PCR (preferred methods) Differential diagnosis includes: Syphilis, chancroid, drug eruptions, Behçet syndrome.</p>	<p>BID-TID, valacyclovir 500 mg BID, or famciclovir 500 mg BID.</p> <ul style="list-style-type: none"> • If lesions persist or recur despite adequate therapy consider resistance testing. Note: most resistance can be overcome with higher doses of acyclovir or valacyclovir. • Famciclovir will likely also be resistant • IV foscarnet is usually effective • During pregnancy, refer to OB/GYN specialist for management. • Counsel use of latex barriers to prevent HSV transmission to uninfected partners.
Genital ulcers	<ul style="list-style-type: none"> • Risk factor for HIV acquisition and transmission. • Research indicates prevalence as high as 14% in an urban population with recurrence rate of 19%. • Only 40% of cases had identifiable pathogen. • Differential diagnosis includes syphilis, chancroid, HSV (see above) all of which may be caused by atypical pathogens identified (CMV, Chlamydia trachomatis, Gardnerella vaginalis). 	<p>Initial episode:</p> <ul style="list-style-type: none"> • Attempt to establish a diagnosis: laboratory testing (viral, bacterial culture, serology) or biopsy. • For severe or erosive lesions, prompt evaluation and management, may necessitate hospitalization and surgery. More aggressive management may be needed to prevent scarring, vaginal or urethral stricture, or fistulae. • Follow up carefully to evaluate for recurrence.

Infection	Epidemiology and Diagnosis	Management
-	<ul style="list-style-type: none"> In women, genital ulcers often are not noticed. Lesions may be large, requiring multiple admissions and surgical procedures. 	-
Bacterial vaginosis (BV)	<ul style="list-style-type: none"> Risk factor for HIV acquisition and transmission. Women infected with HIV have increased persistence of BV, especially with CD4 counts of <200 cells/μL. Bacterial vaginosis is strongly associated with vitamin D deficiency <p>Diagnosis</p> <ul style="list-style-type: none"> Gram stain is gold standard. Clinical criteria: (3 of 4 Amsel criteria): <ul style="list-style-type: none"> Homogeneous, thin, grayish-white discharge that smoothly coats the vaginal walls. Vaginal pH >4.5. Positive whiff-amine test, defined as the presence of a fishy odor when 10% KOH is added to a sample of vaginal discharge. Clue cells on saline wet mount. 	<ul style="list-style-type: none"> Metronidazole 500 mg BID for 7 days Topical vaginal therapy <ul style="list-style-type: none"> Metronidazole gel 0.75%, 5 g QD for 5 days Clindamycin cream 2%, 5 g QD for 7 days <p>Alternatives:</p> <ul style="list-style-type: none"> Tinidazole 1 g PO for for 5 days Clindamycin 300 mg PO BID for 7 days (less evidence for efficacy; higher risk for Clostridium difficile) Clindamycin ovules 100 mg intravaginally QHS for 3 days Consider screening for vitamin D deficiency in patients with intractable BV.
Vaginal candidiasis	<ul style="list-style-type: none"> Women infected with HIV may have higher rates of persistence and recurrence (≥ 4 episodes per year). <p>Diagnosis: Budding yeast and hyphae on 10% KOH wet mount of vaginal discharge.</p>	<ul style="list-style-type: none"> Single episode: <ul style="list-style-type: none"> Topical azoles for 3-7 days Fluconazole 150 mg PO for 1 dose Alternative: Itraconazole 200 mg solution PO daily for 3-7 days Severe or recurrent episodes (≥ 4 episodes per year): <ul style="list-style-type: none"> Fluconazole 100-200 mg PO daily or tropical

Infection	Epidemiology and Diagnosis	Management
-	-	antifungals for ≥ 7 days • Suppressive therapy: fluconazole 150 mg once weekly
Pelvic inflammatory disease (PID)	<ul style="list-style-type: none"> • Among women with HIV infection, risk for severe morbidity and mortality is increased and PID may be more severe at time of presentation. • A Kenyan study showed increased incidence of tubo ovarian abscesses in HIV-infected women. • Women infected with HIV with PID respond to the same antibiotics as women uninfected with HIV but may need surgical interventions more frequently. • Causative organisms include Chlamydia trachomatis, Neisseria gonorrhoea, Streptococcus spp, Escherichia coli, Klebsiella spp, Proteus spp, and BV flora. • Risk factors: Multiple partners, partner with an STD or STD symptoms, prior STD, IUD in situ. • Clinical presentation: Bilateral lower abdominal pain, often <2 weeks' duration, worse with coitus or jarring movements. <p>Clinical diagnosis:</p> <ul style="list-style-type: none"> • Lower abdominal pain, plus one of the following: <ul style="list-style-type: none"> • Cervical motion tenderness or uterine/adnexal tenderness • Temperature $> 101^{\circ}\text{F}$ ($> 38.3^{\circ}\text{C}$) • Leukocytosis • Abnormal cervical or vaginal 	<ul style="list-style-type: none"> • Consider hospitalization in event of severe illness, pregnancy, lack of response, nonadherence, complicated PID with pelvic abscess, need for surgical intervention, or inability to take oral therapy. <p>Outpatient treatment:</p> <ul style="list-style-type: none"> • Ceftriaxone 250 mg IM for 1 dose, plus doxycycline 100 mg PO BID for 14 days, with or without metronidazole 500 mg PO BID for 14 days. • Cefoxitin 2g IM for 1 dose with probenecid 1g PO for 1 dose, plus doxycycline 100 mg PO BID for 14 days, with or without metronidazole 500 mg PO BID for 14 days. • Other parenteral third-generation cephalosporins may be used in place of ceftriaxone or cefoxitin. • Consultation with OB/GYN is recommended as treatment failures, delayed diagnosis, and loss to follow-up are common.

Infection	Epidemiology and Diagnosis	Management
-	mucopurulent discharge <ul style="list-style-type: none"> • Presence of WBCs on saline microscopy of vaginal secretions • Presence of WBCs on saline microscopy of vaginal secretions • Presence of WBCs on saline microscopy of vaginal secretions • Elevated erythrocyte sedimentation rate • Elevated C-reactive protein • An adnexal mass suggests tubo ovarian abscess • Laparoscopic evaluation is recommended for: <ul style="list-style-type: none"> • Strongly suspected competing diagnosis (e.g., appendicitis) • Acutely ill patients for whom outpatient treatment of PID has failed • Patients not clearly improving after 72 hours of inpatient treatment for PID 	-

STD treatments reflect current CDC guidelines.



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Comorbid Conditions

Anal Dysplasia

KEY POINTS

- Patients who are HIV-infected are at much higher risk of developing squamous cell cancer of the anus (SCCA) than the general population and have a poorer 5-year survival rate once it is diagnosed.
- At-risk populations include all men and women who are HIV-infected, particularly men who have sex with men (MSM) (with or without HIV infection), HIV-infected transgender women (TGW), any patient with a history of anogenital condyloma, and women with abnormal cervical or vulvar histology.
- All at-risk men and women should be screened for anal cancer at baseline and annually thereafter by digital rectal examination (DRE). Some specialists recommend an anal PAP smear, if available, at baseline and annually thereafter.
- All patients with abnormal cytology of any degree should be referred for high-resolution anoscopy (HRA) and biopsy.



BACKGROUND

- Anal cancer is increasing in incidence in the past 3 decades. About 5,229 anal cancers are diagnosed annually in the U. S.
- Anal dysplasia refers to precancerous changes in the squamous cells lining the anus. Neoplastic changes begin in the basal cell layer of the anal squamous epithelium, at the transformation zone. If untreated, anal dysplasia may progress over time to SCCA.
- Over 90% of anal cancers are believed due to human papillomavirus (HPV) infection, with 79% caused by HIV types 16 and 18.
- Anal HPV infection and dysplasia are analogous to cervical infection, anal dysplasia, oncogenic HPV types, and SCCA. HPV infection and dysplasia; much of the model for evaluation and management of SCCA is based on cervical cancer screening and management. However, no large studies to date have shown that detection and treatment of precancerous anal lesions prevent anal cancer.
- HIV infection is associated with increased rates of anal HPV and HPV infection may increase susceptibility to HIV infection.

Veterans with HIV*

Malignancy/anal dysplasia: 2%

* Comorbid conditions for Veterans who are HIV-positive in VHA care. Based on Veterans with HIV/AIDS in VHA care with these criteria: (1) At least one ICD9/ ICD10 code consistent with HIV diagnosis. 2) Seen July 2016-June 2017 during at least one inpatient or outpatient visit.

Note: Some medications mentioned in this chapter may not be available on the VHA National Formulary (<https://www.pbm.va.gov/NationalFormulary.asp>). Consult VA pharmacists for alternatives.

- Patients with HIV are more likely to be infected with multiple HPV strains; HPV16 is the most carcinogenic HPV type in the anus.
- In one study, a lower prevalence of anal HPV infection was observed in MSM who are HIV-positive receiving ARV therapy compared to MSM who are HIV-positive not receiving ARV therapy. Immune reconstitution by ARV therapy in MSM who are HIV-positive enhanced the immune response against HPV by increasing titers of anti-HPV antibodies.
- In patients with HIV, current CD4 count and nadir CD4 count are associated with SCCA incidence; the strongest predictor for SCCA is a low CD4 count 6-7 years prior to diagnosis (Odds Ratio = 14 for CD4 count <200 vs. CD4 count >500).
- The risk of high grade anal dysplasia is increased by a history of other sexually-transmitted infections, especially gonorrhea, HSV-2, hepatitis B, and syphilis.
- The relative risk of SCCA among patients who are HIV-infected compared with the general population ranges from 33 to 222, depending on the cohort.
- The rate of SCCA is 2-3 times higher in MSM who are HIV-infected than in MSM who are HIV-uninfected.
- Transgender women remain an underrepresented population in many studies, but 19% of TGW are HIV infected, as well as significantly burdened by HPV infection regardless of coincident HIV infection. Gender-reassignment may or may not play a role in the incidence of anal dysplasia, and it is not known whether estrogen therapies may increase the risk or progression. A study comparing 22 TGW with HIV infection and 1448 MSM with HIV infection reported a similar incidence and severity ranges of anal dysplasia in both groups, suggesting that the risk and incidence of anal dysplasia should not be underestimated in this group.
- Patients who are HIV-infected with SCCA are an average of 10 years younger at presentation than patients who are HIV-uninfected with SCCA.
- A higher prevalence of anal HPV was observed in women who are HIV-infected compared to high-risk women who are HIV-negative (43% vs. 24%). Furthermore, the prevalence of HPV was higher in the anus than in cervix (79% vs. 53%) and was associated with the presence of cervical HPV versus a history of receptive anal intercourse.
- Risk factors associated with the development of anal cancer include receptive anal intercourse (before the age of 30); lifetime number of sexual partners; female gender; current cigarette smoking; genital warts; immunosuppression (organ transplantation and HIV infection); history of other sexually transmitted infections (STIs) or anal fistulae.

- Patients who are HIV-infected with SCCA have similar treatment responses compared with patients who are HIV-uninfected but have an increased risk of recurrence.
- The time course for the development of SCCA from dysplasia is slow; in one study, 40 men who were HIV-positive with untreated dysplasia were followed for 130 months and three patients developed SCCA, a 7.5% progression rate over 11 years. In another study of patients who were HIV-positive with known high-grade dysplasia, 11% developed SCCA within 7 years.
- The long lead time between HPV infection and the development of cancer potentially allows for screening and intervention. However, the value of screening for and early treatment of anal dysplasia is still under investigation.
- Studies indicate rising rates of anal cancer in the HAART era due to, at least in part, the longer life expectancies of patients who are HIV-infected.
- It is important for clinicians to proactively discuss issues of anal health, because patients, especially women and heterosexual men, may be reluctant to broach the topic.



EVALUATION

<p>Risk factors for patients who are HIV-infected at highest risk of HPV infection and anal Dysplasia</p>	<ul style="list-style-type: none"> • MSM • Patients with a history of anal receptive intercourse • Patients with a history of anogenital condylomas • Women with abnormal cervical or vulvar histology • Transgender women • Smokers • Patients with a history of other STIs
<p>Symptoms</p>	<ul style="list-style-type: none"> • Rectal bleeding is present in 45% of patients with SCCA. • Sensation or pain associated with a rectal mass is present in 30% of patients with SCCA; pain may occur with defecation or with receptive anal intercourse. • Pruritus or anal discharge is present in 25% of patients with SCCA. • Up to 56% of early anal cancers detected by clinicians were asymptomatic. Dysplasia usually is asymptomatic.

Physical Examination

- Check perianal skin for external lesions.
- Conduct DRE to check for masses and other lesions.
- Check inguinal lymph nodes for enlargement suggesting dissemination (hard, fixed, progressive).



SCREENING

Summary of Evaluation for Anal Dysplasia

At baseline and annually: Ask about symptoms (e.g., mass, rectal bleeding, pain with defecation or anal receptive intercourse). In patients with anal dysplasia, anal bleeding was more than twice as common in patients who progressed to anal cancer than those who did not (83% vs. 38%).

- Examine perianal skin and inguinal lymph nodes.
 - Certain anal lesion characteristics are associated with progression to cancer, including ulceration or granular texture of lesion (versus smooth).
- Screen for dysplasia: anal PAP test (where available) using smear or liquid cytology. See below.
- Screen for cancer: DRE.

Note: Anal PAP smears should be performed before conducting DRE to avoid contamination of PAP smear with lubricant.

- Routine screening for anal neoplasia is not yet universally adopted for a number of reasons:
 - There is a lack of randomized controlled trials demonstrating that early diagnosis and treatment of anal intraepithelial neoplasia (AIN) leads to decreased rates of anal cancer.
 - Infrastructure for reading anal PAP smears, and for evaluating and treating abnormal anal findings, is not available in many clinics.
 - The sensitivity and specificity for anal PAP smears have been variable. The sensitivity of anal PAP smears has ranged from 69% to 93% and the specificity has ranged from 32% to 59%, compared with diagnosis by HRA-directed biopsy samples. This poor correlation between PAP smear results and biopsy results necessitates that high-resolution anoscopy be available to follow up abnormal PAP smear findings and evaluate for high-grade dysplasia.
 - Treatments for HIV-related anal dysplasia have shown mixed efficacy.
- However, accumulating evidence and clinical experience support screening for and treatment of precancerous lesions.
 - Cohort studies show that early detection of anal dysplasia may be beneficial because identification and treatment of small, localized lesions lead to better morbidity and mortality outcomes.

- A recent analysis of SCCA outcomes in the general population showed that the 5-year survival rate for patients with local disease was 78%, compared with 56% for those with regional disease and 18% for those with distant disease.
- Anal cytology has a sensitivity of 47 to 90% and specificity of 16 to 92%. A significant number of cases detected by cytology are upgraded when the biopsy is obtained. Thus, treatment decisions should be based on the biopsy, not the cytology.
- One small study showed that early detection of anal dysplasia with anal PAP smears was cost-effective.

Anal Cytology (PAP) tests: Currently, there are no universally adopted guidelines for anal dysplasia screening. Many specialists recommend screening all at-risk men and women at baseline and (if normal) annually thereafter.

Anal PAP Test Procedure

- Moisten and insert a Dacron (polyester) swab into the anal canal about 4-5 cm (past the anal sphincter and transformation zone), rotate around the anus to collect cells while removing the swab, while maintaining gentle pressure against the anal canal. Proceed to slide or liquid prep:
 - **Glass slide prep cytology:** Rotate the swab on labeled glass slide, apply fixative, and allow it to dry.
 - **Liquid prep cytology:** Insert the swab into the liquid fixative, swirl around for 15 seconds, remove, and cap the jar. This method avoids drying artifacts.

Note: An anal PAP test must be performed before insertion of lubricant into the anus, because lubricating jelly interferes with smear interpretation. In addition, patients should refrain from using enemas or engaging in receptive anal intercourse for 24 hours before an anal PAP test is performed.

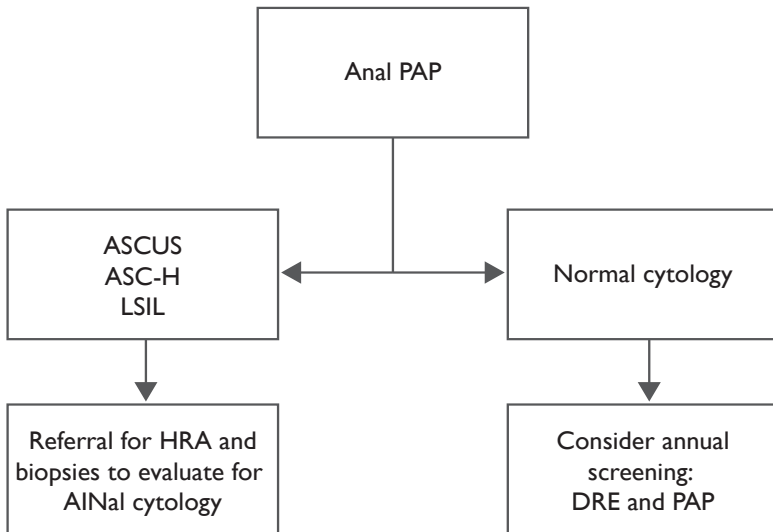
Anal PAP smears should be read by a pathologist trained in their interpretation. Anal cytology is generally graded using Bethesda 2001 criteria, which are ordered as follows:

- Negative for intraepithelial lesion or malignancy
- Atypical squamous cells of undetermined significance (ASCUS)
- Atypical squamous cells cannot exclude HSIL (ASC-H)
- Low-grade squamous intraepithelial lesion (LSIL)
- High-grade squamous intraepithelial lesion (HSIL)
- Squamous cell carcinoma of the anus (SCCA)

LSIL is sometimes referred to as grade 1 anal intraepithelial neoplasia (AIN 1), whereas HSIL may be referred to as AIN 2 or 3, carcinoma in situ, or Bowen disease.

Management

Management of Abnormal PAP Results



- Any patient with abnormal cytology (ASCUS, ASC-H, LSIL, HSIL) should be referred for HRA and biopsy of visible lesions.
- HRA is a technique similar to colposcopy. When 3% acetic acid is applied to the anal mucosa, dysplastic areas will turn whitish (acetowhitening). Lugol's solution is then applied; lesions which do not stain with Lugol's solution are more likely to be HSIL. Lugol's solution is best used in conjunction with acetic acid. Suspicious areas are biopsied and areas of HSIL are eliminated. HRA correctly determines normal mucosa 90% of the time and HSIL 75% of the time when compared with biopsy. HRA is more likely to miss low grade dysplasia.
- Note that ASCUS and LSIL findings on cytology do not rule out the presence of HSIL or cancer; follow-up evaluation with HRA is important, especially given the known discordance between cytology and biopsy results.
- If HRA is not available at a local VA facility, one option is to refer the patient to a local non-VA provider on a fee basis; a list of anal dysplasia specialists in the United States can be found on the UCSF HRA Provider List webpage, <http://analcancerinfo.ucsf.edu/hra-provider-list>.
- If HRA cannot be obtained, regular anoscopy can be performed to look for visible lesions. Biopsy should be performed on lesions to determine the degree of histologic changes and rule out invasive cancers. Note that anoscopy is likely to be insensitive.

- The current recommendation by the American Society of Colon and Rectal Surgeons is that patients with AIN undergo surveillance with digital rectal exam, standard anoscopy or HRA every 3 to 6 months as long as dysplasia is present, with biopsies as indicated. If no dysplasia is present, the follow-up period may be extended. High-risk patients (HIV infection, transplant, and MSM) require closer surveillance.

Treatment

Currently, there are no consensus treatment guidelines. The treatment options presented here are based on expert opinion. The decision to treat should be based on biopsy (not cytology) results.

The focus of treatment is **on high-grade, precancerous lesions. Most experts agree AIN grade 2 or 3 lesions should be treated. Lower-grade lesions typically are monitored with serial HRA exams.**

In a study of the treatment of AIN that compared imiquimod (Iq), topical fluorouracil (TF), and electrocautery (Ec), a complete response was observed in 24, 17, and 39% in the three groups, respectively. Recurrence was observed at 72 weeks in 71, 58, and 68% of the Iq, TF, and Ec groups, respectively. Grade 3-4 side effects (primarily pain, bleeding, or itching) were noted 43, 27, and 18% in the Iq, TF, and Ec groups, respectively. Thus, none of the treatments gave a high response rate and all were prone to recurrences; Ec was the best tolerated.

Biopsy Findings	Treatment Options
Low-grade lesions (AIN 1)	<ul style="list-style-type: none"> • Monitor via HRA every 6 months until normal twice in succession, then annual PAP smear. • Topical treatment may be indicated for symptoms such as bleeding, itching, or burning; or for discrete lesions. See below.
High-grade lesions (AIN 2 or 3)	<p>Topical therapy: For small lesions (<1 cm² at the base)</p> <ul style="list-style-type: none"> • Local application of bichloroacetic acid or 80-90% trichloroacetic acid (well-tolerated but occasionally painful) • Liquid nitrogen • Other topical, self-applied options studied in small cohorts include: <ul style="list-style-type: none"> • Topical imiquimod applied for 6-10 hours then washed off, three times a week for 16 weeks • Topical 5% topical 5-fluorouracil applied twice weekly for 16 weeks • These sometimes are used to treat diffuse lesions. <p>Infrared coagulation ablation: (office-based)</p> <ul style="list-style-type: none"> • For lesions too large for topical therapy

Biopsy Findings

Treatment Options

-	<ul style="list-style-type: none"> • Followed by debridement of destroyed tissue using biopsy forceps • Note: this treatment is not yet FDA approved. <p>Surgery and CO₂ laser ablation:</p> <ul style="list-style-type: none"> • For large (>1 cm²) or extensive lesions, or for patients unable to receive infrared coagulation • Surgical excision with a scalpel for discrete lesions with or without laser ablation • Large lesions may require multiple, staged procedures to reduce risk of bleeding, anal stenosis, sphincter compromise, and infection. • Referrals should be made to surgical centers with experience in treating anal dysplasia. • High-grade squamous intraepithelial lesions recur in about 60–70% of patients within 1 year after ablation. <p>Follow-up HRA should be done every 6 months. Because HSIL treatment may be associated with morbidity, some have suggested delaying HSIL treatment and monitoring patients until the occurrence of early invasive cancer, which is very treatable, with a five-year cancer-specific survival of 95%.</p>
SCCA	<p>Full discussion of anal cancer is beyond the scope of this chapter; but special points are noted below:</p> <ul style="list-style-type: none"> • Clinical staging consists of physical examination and biopsy of the primary tumor, palpation of the groin, CT of the chest, and CT or MRI of the abdomen and pelvis. • Staging is based on size of tumor (T1-4) and node positivity (N0-1, 2-3 for nodal metastases) and correlates with 5-year survival rate. • First-line treatment consists of chemoradiotherapy rather than surgery. • Delays in diagnosis and treatment of SCCA may necessitate more aggressive treatment, which may result in significant morbidity including infection, bleeding, anal stenosis, and need for colostomy. • Each 100-cells/mm³ decrease in post-treatment CD4 count increased the risk of recurrence by 54%.

Prevention

The 9-valent HPV vaccine (Gardasil 9) is FDA approved for use in males and females aged 9-26 to prevent anal cancer, as well as to prevent cervical cancer and genital warts. The 9-valent vaccine covers types 6, 11, 16, 18, 31, 33, 45, 52, and 58, which cause 90-95% of anal cancers. The immunogenicity of the HPV

vaccine is comparable in patients with HIV and patients who are uninfected. The older quadrivalent HPV vaccine showed 26% efficacy for the prevention of squamous intraepithelial lesions and a 50% lower HSIL recurrence rate in HIV-negative MSM. The HIV load at the time of the first dose of HPV vaccine is the major predictor of anti-HPV antibody titers, regardless of the CD4 count. Further evaluation of the efficacy and safety of HPV vaccination in patients who are HIV-infected, including those over the age of 26, is ongoing.

Future Directions

- The efficacy of anal HSIL treatment may be improved by the use of post-treatment adjuvant HPV vaccination because it decreases the risk of recurrence and thus may decrease progression to SCCA.
- One study indicates that men can be trained to do a self-anal examination or partner anal examination. Tumors of ≥ 3 mm may be detected accurately by these exams; early detection is important because there is a high cure rate for SCCA tumors ≤ 10 mm.



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Androgen Deficiency

KEY POINTS

- Androgen deficiency is relatively common among patients with HIV, although its prevalence has decreased as ARV therapy use has increased.
- Manifestations of HIV-associated androgen deficiency can include loss of muscle mass, fatigue, depression, gynecomastia, testicular atrophy, difficulty concentrating, osteopenia, anemia, insulin resistance, reduced body hair, erectile dysfunction, and reduced functional status.
- Testosterone replacement can alleviate these symptoms to varying degrees.
- Men with low-normal serum testosterone but symptoms of androgen deficiency may benefit from replacement therapy.
- Most men with HIV infection and androgen deficiency will have the hypogonadotropic variant rather than testicular failure; measuring follicle-stimulating hormone (FSH) and luteinizing hormone (LH) can help distinguish between the two types.
- The use of testosterone replacement in women with HIV-associated wasting remains under studied but appears to be generally well tolerated.



BACKGROUND

- Androgen deficiency is defined as subnormal testosterone production with associated symptoms. Hypogonadism is a more general term that refers to deficient sex hormone production; in men, it refers to defective testosterone production, whereas in women, it refers to defective estrogen production.
- This chapter will address testosterone deficiency in adults with HIV; for information on female hypogonadism. See **Women's Health**, p. 283.
- Mechanisms may be *primary* (testicular) or *secondary* (hypothalamic/pituitary).
 - Primary (hypergonadotropic) androgen deficiency: low testosterone (free, bioavailable, or total) + elevated FSH and/or LH.
 - Secondary (hypogonadotropic) androgen deficiency: low testosterone (free, bioavailable, or total) + low or inappropriately normal FSH and/or LH.
- Most men who have HIV (up to 75%) with decreased testosterone levels have secondary (i.e., pituitary) androgen deficiency.
- Up to 50% of men with AIDS-related wasting had abnormally low testosterone levels in studies done before the availability of effective ARV therapy. Many women with HIV also have subnormal androgen levels. Note that normal testosterone levels in women are approximately one tenth those in men.

Note: Some medications mentioned in this chapter may not be available on the VHA National Formulary (<https://www.pbm.va.gov/NationalFormulary.asp>). Consult VA pharmacists for alternatives.

- The prevalence of androgen deficiency has declined with the use of ARV-therapy, but remains substantial: Up to 20% of men on ARV therapy with less-than-ideal body weight have abnormally low free testosterone.
- Androgen deficiency is relatively common even in younger men who are HIV-positive with good virologic control. In a 2017 study of 113 virologically suppressed HIV-positive men under 50 years of age, with an average CD4 count of 634 cells/mm³, 12.4% had androgen deficiency, twice the rate of the general population for this age group. Factors associated with androgen deficiency included total body fat, length of exposure to ARV therapy, and exposure to integrase inhibitors.
- Manifestations in men include reduced muscle mass, decreased strength, fatigue, depression, difficulty concentrating, decreased libido, oligospermia, decreased erectile function, reduced functional status, anemia, testicular atrophy, and bone loss.
- One study found that 100% of HIV-positive men with hypogonadism had erectile dysfunction (ED), but only one quarter of the patients with ED were hypogonadal; the causes of ED in men with HIV are multifactorial.
- Hypogonadism in patients with HIV is associated with multiple comorbidities; it is uncertain if poor health status induces hypogonadism or if testosterone deficiency promotes the onset of comorbidities. Higher levels of frailty are associated with low serum testosterone levels.
- Manifestations in women are less studied, but include fatigue, anemia, decreased libido, and wasting.
- Treatment of hypogonadal men who are HIV-infected with testosterone can lead to increased muscle mass and quality of life, and improvements in depression. In women, treatment has shown increase in weight and social functioning.

Possible causes of androgen deficiency in men with HIV include:

- HIV infection (mechanism unclear)
- Hepatitis C
- Cirrhosis
- Medications/drugs (e.g., opiates, glucocorticoids, ketoconazole, anabolic steroids, megestrol, or testosterone)
- Illicit drug use (marijuana, opiates, cocaine)
- Tumors, infection, or infiltration of the hypothalamus or pituitary gland
 - In addition to endocrine abnormalities, symptoms may include headaches, seizures, visual disturbances (temporal field cuts, diplopia)
 - Prolactinoma
 - Metastatic disease
 - Granulomatous disease
 - Abscess
- Radiation therapy, chemotherapy

- Trauma
- Malnutrition



EVALUATION

Note: Onset can be subtle and symptoms may be attributed to other causes (“getting older;” primary depressive disorder, anxiety, chronic illness)

Symptoms	<ul style="list-style-type: none"> • Loss of libido • Weight loss, especially of lean muscle mass • Erectile dysfunction • Oligospermia/decreased ejaculate volume • Depressive symptoms, poor concentration • Fatigue • Infertility
Physical Examination	<p>To include assessment of muscle mass, secondary sexual characteristics. Check for:</p> <ul style="list-style-type: none"> • Visual fields (to evaluate for pituitary lesion impairing optic nerve) • Small or soft testes (size smaller than approximately 4.5-6.5 cm long × 2.8-3.3 cm wide; suggests atrophy) • Testicular masses (roll each testicle between thumb and 1st two fingers, feeling for fixed or firm masses, which may not be tender) • Gynecomastia; suggests primary androgen deficiency if FSH or LH is elevated
Laboratory Evaluation	<p>Laboratory measurements to evaluate androgen deficiency are imperfect. Total testosterone reflects all circulating testosterone components: free (unbound) testosterone + testosterone bound (loosely) to albumin and (tightly) to sex hormone-binding globulin (SHBG). Only free testosterone and albumin-bound testosterone are bioavailable. SHBG increase with HIV infection, old age, hypothyroidism, liver disease, and androgen deficiency itself, thus increasing the total testosterone measured while potentially decreasing the amount of unbound (active) testosterone. Obesity, diabetes and insulin resistance are common causes of reduced SHBG.</p> <p>Total testosterone is a reasonable initial screening test that should be conducted between 8 am and 10 am and repeated to confirm low testosterone. Determination of free testosterone by equilibrium dialysis is considered the gold standard, but is not available in many laboratories. Nevertheless, the measurement of free testosterone is preferable in men who are HIV-infected due to increases</p>

in SHBG. Using total testosterone instead of free testosterone may miss half of cases of androgen deficiency in men with HIV.

Acute illness may cause transient secondary hypogonadism; thus, investigation for hypogonadism should be delayed until the acute illness has resolved.

Initial evaluation:

- Serum testosterone: morning blood sample for total testosterone or preferably, free testosterone (if available)
 - Average serum testosterone levels decrease with age, and there is no absolute cutoff dividing normal from subnormal serum testosterone. One approach to determining testosterone deficiency is to define normal as >2.5 standard deviations below the mean serum total testosterone of healthy young males (approximately 319 ng/dL, per the American Association of Clinical Endocrinologists [AACE]).
 - If total testosterone level is below or near normal, most authorities recommend rechecking total testosterone and measuring free testosterone (by equilibrium dialysis, if feasible, or by free testosterone concentration) or bioavailable testosterone. The analog method of measuring free testosterone is not recommended.
- FSH, LH to distinguish primary from secondary androgen deficiency.

Other tests:

- Other pituitary hormone levels (prolactin, growth hormone, TSH), if hypopituitarism (hormone levels low) or pituitary adenoma (hormone levels high) is suspected.
- Sperm count and motility, if fertility is an issue.
- Consider MRI if workup suggests hypothalamic or pituitary mass or other abnormality (e.g., abnormal pituitary hormone levels, visual field lesions, or neurologic signs).
- Testicular ultrasound if testicular masses are detected on examination.

R_x MANAGEMENT

- Evaluate and treat potential reversible causes of androgen deficiency. Note that in patients with advanced HIV disease, effective ARV therapy may reverse androgen deficiency over months of treatment.
- For men with documented androgen deficiency (signs and symptoms with abnormal total testosterone, usually <200-320 ng/dL, or free testosterone, usually <6.5 ng/dL), testosterone is the preferred treatment.

- Some authorities recommend testosterone replacement therapy in men with symptoms of androgen deficiency, but low-normal testosterone levels. See **Symptoms**, above.
- Typical recommended dosages for men. Note that testosterone is classified as a Schedule III drug by the U.S. Drug Enforcement Agency.
 - IM testosterone undecanoate:
 - 750 mg followed by 750 mg injected after 4 weeks, then 750 mg every 10 weeks thereafter
 - IM testosterone (cypionate or enanthate):
 - 100 mg IM every 7 days
 - 200 mg IM every 14 days
 - 300 mg IM every 21 days
 - Longer dosing intervals with higher dosages are more convenient, but risk higher peak levels and greater fluctuations in testosterone level.
 - Cypionate contraindicated in renal or hepatic dysfunction
 - Transdermal (patch) testosterone: 1 patch (5 mg) applied daily
 - May cause skin irritation
 - Testosterone gel: 5 mg applied daily to trunk and shoulders. Patient should be instructed to wash hands thoroughly after application to avoid transfer of gel to others. **Note:** Testosterone gel can be transferred to persons in contact with the treated patient and has been associated with virilization in children and women. Patients should be counseled about the potential effect of testosterone gel in close contacts and to use gel in areas less likely to contact others.
 - Unreliable absorption in some men
 - Transdermal solution: initial dose is 60 mg (1 pump actuation to each armpit); once daily, at same time
 - Deodorant should be applied prior to axillary testosterone
 - Buccal testosterone: 30 mg oral patch applied twice a day
- For women with HIV-associated wasting and subnormal serum testosterone, twice weekly transdermal testosterone (5 mg twice weekly) for 6 months has been studied as a treatment. This treatment resulted in an increase in muscle mass with no significant side effects. There are no firm guidelines for testosterone use in women.
- **Testosterone is absolutely contraindicated in men with prostate cancer or patients with a history of breast cancer;** it should be used with extreme caution in men with benign prostatic hypertrophy, and only after urologic consultation. Urologic consultation is recommended prior to testosterone treatment in those with prostate-specific antigen (PSA) of >4 ng/mL, or >3 ng/mL in patients with higher risk of prostate cancer (e.g., African Americans or patients with a first-degree relative with prostate cancer).

- **Other contraindications**
 - a hematocrit greater than 50%
 - untreated obstructive sleep apnea
 - severe lower urinary tract symptoms
 - class III or IV heart failure
- **Testosterone is absolutely contraindicated in pregnant women because of effects on the fetus.**
- Testosterone therapy usually is well tolerated. Potential adverse effects of testosterone therapy include:
 - Testicular atrophy
 - Hirsutism
 - Gynecomastia
 - Prostatic enlargement and unmasking of occult prostate cancer
 - Acne
 - Mood swings (especially with high doses of IM testosterone)
 - Polycythemia (more common with IM testosterone)
 - Elevations in ALT,AST
 - Dyslipidemia
 - Skin irritation at patch site
 - Sleep apnea (rare)
 - Myocardial infarction (controversial; carefully weigh benefit vs. risk in patients with high baseline cardiovascular risk)
 - In women, testosterone may also cause virilization; start with low doses and monitor closely for adverse effects
- Follow up 2-3 months after starting replacement (AACE):
 - Measure serum testosterone response to check for efficacy of dosage
 - IM testosterone: measure serum testosterone at midpoint between doses
 - Patch: measure 3-12 hours after application
 - Gel: timing not critical, as blood levels are constant
 - Assess for side effects and check hepatic transaminases and hemoglobin/hematocrit; discontinue testosterone if hematocrit >54%.
 - In case of adverse effects, discontinue or lower the dosage of testosterone.
 - With the IM formulation, may consider switching to a transdermal formulation, which gives more even dosing and avoids high peak testosterone levels. May also consider switching from high-dose/less-frequent administration to lower-dose/more-frequent administration.
 - Testosterone therapy may unmask occult prostate cancer. Examine the prostate every 6-12 months, looking for prostatic enlargement; check serum prostate-specific antigen (PSA) in older men.

- If significant enlargement on therapy develops, masses or nodules are detected, or PSA becomes abnormally elevated, discontinue testosterone and refer to Urology for evaluation.
 - Discontinuation of testosterone replacement:
 - There currently are no evidence-based guidelines for discontinuation of testosterone replacement. If the underlying cause of hypogonadism has been addressed (such as effective treatment of HIV), it is reasonable to consider discontinuation of testosterone therapy with monitoring for recurrence of symptoms.

Note: Other anabolic steroids such as oxandrolone, an orally available alkylated androgen, are not recommended in place of testosterone, as they do not have the same effects in the body and may convey higher risk of adverse effects, such as hepatic toxicities (peliosis hepatis, hepatoma, cholestatic jaundice) and lipid derangements. Nandrolone, a parenteral androgen with more anabolic properties than testosterone, is no longer available in the United States.



WHEN TO REFER

Endocrinology	<ul style="list-style-type: none"> • Lack of symptomatic improvement • Diagnostic uncertainty, especially if secondary androgen deficiency remains in differential diagnosis • Evidence of hypothalamic or pituitary mass
Urology	<ul style="list-style-type: none"> • Testicular masses • Prostatic enlargement, masses, or nodules, or elevated PSA



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Bone Health

Bone strength = the capacity of bone to absorb energy without fracturing-determined by bone mineral density (BMD) and bone quality.

KEY POINTS

- **Bone quality** is a function of bone microarchitecture and mechanical properties.
- **Bone Mineral Density (BMD)** is determined clinically by DEXA scanning. See below.
- **Microarchitecture** is determined in research settings by DEXA-based techniques that allow calculation of a trabecular bone score (TBS), a BMD-independent predictor of fracture risk.
- **Mechanical properties** of bone are assessed by microindentation methods. Microindentation determines the resistance to fracture at the tissue level, using a test probe to indent the bone. The deeper the test probe indents the bone, the more easily the bone is fractured.
- **Aging** is the most important determinant of bone strength; fracture risk increases exponentially after age 60 in the general population.



BACKGROUND

HIV and Bone Strength

Patients with HIV commonly have decreased BMD, and other markers of decreased bone strength.

- BMD is 3–5% lower in patients with HIV infection than in uninfected patients. In one study, 67% of adult patients with HIV had reduced BMD.
- Osteoporosis (OP) is 3-4 times more common in patients with HIV as compared to uninfected.
- Especially high risk patients with HIV: men >50 years old and postmenopausal women or patients with a history of fragility fracture; post-menopausal women who are HIV-positive have 3 to 10-times the risk of OP compared to women who are HIV-negative.
- For women, HIV infection results in earlier age of menopause, increasing OP risk.
- There is almost a 20% decrease in bone microarchitectural parameters between long term men infected with HIV and controls.
- Microindentation reveals that the bone of patients with HIV has inferior mechanical properties compared to uninfected persons, regardless of BMD.

Note: Some medications mentioned in this chapter may not be available on the VHA National Formulary (<https://www.pbm.va.gov/NationalFormulary.asp>). Consult VA pharmacists for alternatives.

Fractures are more common in patients with HIV.

- In one meta-analysis, the incidence rate ratio for all fractures was 1.58 for patients with HIV compared with uninfected persons.
- Co-infection with hepatitis C (present in up to 1/3 of Veterans infected with HIV) further increases fracture risk.
- Patients co-infected with HIV/HCV have a three-fold higher fracture incidence compared to uninfected individuals and up to twice the fracture risk of subjects mono-infected with HIV.

Causes of Low Bone Mineral Density in Patients with HIV

HIV itself from immune activation, inflammation

- HIV infection causes suppression of osteoblast activity; stimulation of osteoclast activity.

Antiretroviral treatment generally

- BMD decreases by 2-6% during the first 2 years following ARV therapy initiation, extent varies depending on regimen; after 2 years of ARV therapy, BMD stabilizes.
- Low pre-ARV therapy CD4 count is a risk factor for increased bone loss after ARV therapy initiation.
- For patients starting ARV therapy, calcium/vitamin D supplementation attenuates bone loss.

Specific antiretroviral agents; not observed in all studies. See below.

Other risk factors for osteopenia/osteoporosis common in patients with HIV:

- smoking; opiate and cocaine use; alcohol abuse
- frailty and physical inactivity
- vitamin D deficiency
- chronic kidney disease
- low BMI (<30) or weight loss
- hepatitis B and/or hepatitis C co-infection
- liver cirrhosis with decompensation
- male hypogonadism
- diabetes mellitus
- history of systemic corticosteroid use (>5 mg prednisone/d for >3 months)
- anti-depressant drug use



Effect of Specific Antiretroviral Agents on Bone Health

Tenofovir Disoproxil Fumarate (TDF)

- Affects the BMD and mechanical properties of bones.
- In the EuroSIDA cohort, the incidence of bone fracture among patients exposed to TDF was 40% higher than that of patients never exposed to this drug.
- In one study, initiation of TDF-emtricitabine + lopinavir-ritonavir induced a rapid increase in bone resorption markers.
- Proximal tubular dysfunction leading to phosphaturia is one proposed mechanism of TDF's adverse effect on bone.

Protease Inhibitors (PIs)

- PIs increase the risk of hypothyroidism, which contributes to loss of BMD.
- PIs alter vitamin D metabolism.
- In one study, switching from a PI to an integrase inhibitor lead to a decrease in serum markers of poor bone quality.

Efavirenz (EFV)

- Associated with lower serum levels of 25-hydroxy vitamin D.
- However, EFV has not been associated with lower BMD.
- Patients on TDF-FTC-efavirenz have half the rate of fractures vs. other TDF-FTC containing regimens: TDF-FTC-Protease Inhibitor and TDF-FTC-cobicistat-elvitegravir, likely due to higher levels of TDF when concomitantly used with PI or cobicistat, and the food taken with the latter regimens.

Tenofovir disoproxil fumarate (TDF) vs. Tenofovir alafenamide (TAF)

- In 2016, tenofovir alafenamide (TAF), a novel prodrug of tenofovir, entered the market as a component of three combination antiretrovirals: Descovy (TAF, emtricitabine (FTC)), Genvoya (TAF, FTC, elvitegravir-cobicistat), and Odefsey (TAF, FTC, rilpivirine). TAF has 91% lower plasma tenofovir levels compared with TDF, with reduced adverse effects on bone.

- In a study comparing TAF and TDF (each co-formulated with elvitegravir, cobicistat, and FTC), TAF showed lesser declines in hip and lumbar spine BMD vs. TDF through wk 144 (% change from baseline: hip, TAF -0.75%, TDF -3.36%; spine, TAF -0.92%, TDF -2.95%).
- More patients on TAF recovered from osteopenia or osteoporosis.
- Changes from baseline in serum parathyroid hormone (PTH) were lower with TAF than TDF (wk 144: TAF 47.3%, TDF 71.8%; $P < 0.001$).

Switch Therapy Considerations

Consider modifying antiretroviral therapy in patients on high-risk regimens with reduced BMD or in patients at high risk for reduced BMD due to the other risk factors described above; also, consider modification if safer agents are available, i.e., TAF instead of TDF; unboosted integrase inhibitors instead of PIs.

- TDF-sparing regimens using integrase inhibitors in ARV therapy-naïve patients are associated with decreased BMD loss.
- Switching from TDF-FTC to abacavir-lamivudine is associated with a decrease in bone turnover markers; however, TDF and ABC have the same effects on TBS.

Dual-energy X-ray absorptiometry (DEXA) scans determine BMD by measuring the differential absorption of two X-ray beams of different energies.

- A DEXA scan of the hip and/or spine is the preferred measurement for determining a diagnosis of osteopenia/osteoporosis.
- DEXA scans report T- and Z-scores, the number of standard deviations (SD) that the subject's bone density is above or below a reference population.
- **T-score:** subject's BMD compared to the mean bone density of a young healthy adult population of the same sex and ethnicity.
- **Z-score:** subject's BMD compared to the mean bone density of population of the same age, sex, and ethnicity.
- A T-Score from +1.0 to -1.0 SD vs. the mean of young adult is considered to be normal, while a T-score -1.0 to -2.5 SD indicates osteopenia; below -2.5 SD indicates osteoporosis.
- The FRAX algorithm can be used to estimate the 10-year probability of hip or major osteoporotic fracture; it utilizes age, gender, weight, height, and femoral neck BMD (or BMI), and clinical risk factors. See <https://riskcalculator.fore.org/>.
 - **Clinical Risk Factors Utilized in the FRAX Algorithm**
 - Previous fragility fracture
 - Parental history of hip fracture
 - Current smoking
 - Rheumatoid arthritis

- Secondary osteoporosis
- Alcohol intake ≥ 3 drinks per day
- Oral corticosteroid use

However, the FRAX algorithm has not been validated for patients with HIV and these patients may be at higher risk of fracture than calculated by the FRAX score.



EVALUATION

Assessment of Patients with HIV for Osteoporosis Risk

- Assess risk factors as described above.
- If the history does not reveal specific risk factors for osteoporosis and no history of fractures and if the patient is a male < 50 years of age or a premenopausal female, then the DEXA scan can be deferred.
- If the history indicates risk factors for osteoporosis, or previous fractures, and the patient is a post-menopausal female, or a male greater than age 50, then a DEXA scan is indicated.



MANAGEMENT

FDA-approved medications for the treatment of osteoporosis

Bisphosphonates (alendronate, ibandronate, risedronate, zoledronic acid), calcitonin, estrogens for women, testosterone for men; estrogen agonist/antagonist (raloxifene), parathyroid hormones (PTH, teriparatide), RANKL inhibitor (denosumab).

Other measures: smoking cessation; increased calcium/vitamin D intake and weight-bearing exercise; assessment of fall risk

- Perform vertebral fracture assessment in those with kyphosis, height loss, low vertebral BMD.

Screen for vitamin D deficiency yearly and in high-risk patients.

- Goals: serum level 25-hydroxyvitamin D of 30 ng/mL, normal serum PTH level.
- Treatment: ergocalciferol 50,000 units/week x 12 wks, then 50,000 units/mo or cholecalciferol 10,000 units per day x 8 wks, then 800-2000 units/d.
- Combine with calcium supplement in patients with poor dietary calcium intake.

- Repeat serum level of 25-hydroxyvitamin D soon after loading doses above.



WHEN TO REFER

Indications for consultation with an endocrinologist or rheumatologist:

- Severe osteoporosis
- Significant secondary causes contributing to low BMD
- Treatment intolerance or failure



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KEY POINTS

- Chronic liver disease is common among patients infected with HIV, and is increasingly a cause of mortality and morbidity as effective ARV therapy allows patients with HIV to live longer.
- HIV infection may accelerate liver damage caused by HCV or HBV infection. HCV infection is particularly common among patients infected with HIV, especially those who acquired HIV through injection drug use (IDU).
- Long-term complications of HBV and HCV infection include cirrhosis, end-stage liver disease (ESLD), and hepatocellular carcinoma (HCC).
- It is essential that providers working with patients with HIV be able to identify liver disease and determine whether cirrhosis has developed.
- Long-term management of cirrhosis is important to providing optimal prevention and treatment of complications.
- Some ARVs may cause liver toxicity (hepatotoxicity) but most can be used safely by patients with liver disease, with proper monitoring. Patients should not be undertreated for HIV because of concurrent liver disease.

Note: Current information on VA policy, guidelines, and tools related to liver disease can be found online at <http://www.hepatitis.va.gov/>.



BACKGROUND

Any disease or injury that chronically affects the liver can cause fibrosis; this process ultimately may progress to cirrhosis.

Cirrhosis is characterized by distortion of the hepatic architecture with diffuse interlacing bands of fibrous tissue leading to the formation of regenerative nodules in the hepatic parenchyma.

Epidemiology of HIV and Liver Diseases

- **High morbidity and mortality:** In the U.S. general population, cirrhosis accounts for 40,000 deaths per year and for the loss of more than 228,000 years of potential life. Liver disease is the third leading cause of death in patients with HIV.
- As patients with HIV with access to ARV therapy survive longer, comorbidities such as chronic liver disease have become leading causes of illness and death.
- Depending on the locale, 30-80% of patients with HIV are co-infected with hepatitis C and 5-15% with hepatitis B. HIV infection accelerates

Note: Some medications mentioned in this chapter may not be available on the VHA National Formulary (<https://www.pbm.va.gov/NationalFormulary.asp>). Consult VA pharmacists for alternatives.

progression of liver disease associated with HCV or HBV, and end-stage liver disease (ESLD) is now a leading cause of death in patients with HIV/HCV or HIV/HBV co-infection.

The incidence of hepatic decompensation was greater among HIV/HCV co-infected than HCV mono-infected patients (7.4% vs. 4.8% at 10 years). Co-infected patients with HIV viral loads < 1000 copies/mL still had higher rates of decompensation than mono-infected patients (HR, 1.44). Baseline advanced hepatic fibrosis, hemoglobin level < 100 g/L, diabetes mellitus, and non-black race were associated with higher rates of decompensation among co-infected patients.

- Other factors that cause more severe liver disease, including alcohol abuse, drug-associated hepatotoxicity, male gender, and hepatic steatosis, are also more common in the HIV-infected population.
- Alcohol abuse is a major contributor to liver-related mortality in patients with HIV.

Potential Causes of Liver Disease, Especially among Patients with HIV

Common

- Alcoholic liver disease
- Alcoholic cirrhosis
- Chronic hepatitis B
- Chronic hepatitis C
- Nonalcoholic fatty liver disease (NALFD)

Less Common

- Drug-induced liver injury, including by ARV agents
- Autoimmune hepatitis
- Primary biliary cholangitis
- Primary sclerosing cholangitis
- Genetic: Hemochromatosis, Wilson disease, Alpha-1 antitrypsin deficiency

Prevalence of Viral Hepatitis among Individuals with HIV in the United States

- 30-80% co-infected with HCV
 - 9-27% of heterosexuals
 - 1-12% of men who have sex with men
 - 72-95% of injection drug users

- 31% of Veterans
- 5-15% co-infected with HBV
 - 4-6% of heterosexuals
 - 9-17% of men who have sex with men
 - 7-10% of injection drug users
 - 14% of Veterans
- Risk factors for liver diseases other than viral hepatitis are common in the HIV-infected population.
- Abnormal liver enzyme levels are common among patients infected with HIV, even without HCV or HBV infection.
 - Cross-sectional studies have shown a high prevalence of elevated AST (20%), ALT (15%), and alkaline phosphatase (43%).
- Alcohol consumption is common among patients infected with HIV.
 - Rates of heavy drinking among people with HIV are almost double those in the general population. Approximately 8% of persons with HIV report heavy drinking in the past month.
 - Alcohol use disorders were diagnosed in 33% of Veterans infected with HIV in VA care in 2007.
- Other comorbidities associated with liver disease:
 - Diabetes mellitus, Hyperlipidemia, Obesity, Hemophilia, Ulcerative colitis

Nonalcoholic Fatty Liver Disease (NAFLD)

- NAFLD refers to fat deposition in hepatocytes (steatosis), in individuals without alcohol use. When accompanied by inflammation and fibrosis, it is referred to as nonalcoholic steatohepatitis (NASH).
- The prevalence of NAFLD in the U.S. population ranges from 17-33%, and risk factors include obesity, hyperglycemia, diabetes mellitus, and hypertriglyceridemia (metabolic syndrome).
- The prevalence of hepatic steatosis in patients infected with HIV is high, especially in those with chronic hepatitis C or on NRTIs. In individuals co-infected with HIV/HCV, rates of steatosis range from 40-69%.
- In the general population, approximately 10-15% of patients with steatosis progress to NASH, and 15-20% of these patients progress to cirrhosis. In subjects co-infected with HIV/HCV, hepatic steatosis has been associated with more advanced liver fibrosis.



EVALUATION

- At initial assessment, patients infected with HIV should be evaluated for clinical, biochemical, and virologic evidence of chronic liver disease.

- Frequency of reassessments depends on the presence and severity of existing disease, risk factors for liver disease (e.g., IDU, alcohol abuse), and prescription of potentially hepatotoxic medications (e.g., nevirapine; mitochondrial toxic nucleoside reverse transcriptase inhibitors (stavudine, zidovudine, didanosine)).

Clinical Features of Liver Diseases

See below for features of decompensated cirrhosis.

History	<p>More than 40% of patients with cirrhosis are asymptomatic.</p> <ul style="list-style-type: none"> • Fatigue is the most common initial symptom of chronic viral hepatitis • Anorexia, weight loss • Inability to concentrate, sleep disturbances, confusion • Testicular atrophy, decreased libido, impotence in men; chronic anovulation in women • Pruritus (in cholestatic liver diseases)
Physical Examination	<p>Perform a physical examination with special attention to the abdomen, skin, and neurologic system. Note that patients may display no abnormalities. Abnormal findings suggestive of cirrhosis include: jaundice, asterixis, spider angiomas, gynecomastia, Palmar erythema, Testicular atrophy, Caput medusa, Temporal wasting, palpable left liver lobe, splenomegaly, ascites, clubbing, hypertrophic osteoarthropathy, Dupuytren contracture, Feter hepaticus.</p>

ARVs and Hepatotoxicity

Metabolic abnormalities are extremely common in patients infected with HIV on ARV, especially NRTI-PI combinations. These include insulin resistance, dyslipidemia, hypertriglyceridemia, and lipodystrophy.

Many ARVs may cause liver damage, particularly in patients with preexisting liver disease. These include:

- Nevirapine*
- Most PIs, particularly darunavir, tipranavir
- Stavudine, didanosine, zidovudine

Note: Atazanavir (ATV) and Indinavir (IDV) may cause isolated hyperbilirubinemia through inhibition of uridine diphosphate-glucuronosyltransferase (UGT) activity; this does not indicate liver damage.

* Increased risk if NVP is initiated in men with CD4 counts >400 cells/ μ L or in women with CD4 counts >250 cells/ μ L.

Biochemical Features of Liver Disease and Common Causes

Elevated Aminotransferases (AST,ALT)	Elevated Alkaline Phosphatase (with or without bilirubin elevation)	Elevated Bilirubin (without increase in alkaline phosphatase)
<ul style="list-style-type: none"> Chronic HCV Chronic HBV Autoimmune hepatitis Nonalcoholic steatohepatitis (NASH) Drug-induced liver injury (DILI), e.g., alcohol 	<ul style="list-style-type: none"> Primary biliary cholangitis Primary Sclerosing cholangitis DILI Infiltrative liver disease Sarcoidosis Granulomatous hepatitis Drug effect: tenofovir disoproxil 	<ul style="list-style-type: none"> Cirrhosis Drug effect (e.g.,ATV and IDV commonly cause isolated elevation of unconjugated bilirubin)

Note: A Web-based course on liver function test abnormalities is available at <https://www.hepatitis.va.gov/course/index.asp?page=/provider/courses/livertests/livertests-toc&>

Laboratory Findings and Specific Liver Diseases

Disease	Typical Findings (may not be present)
Alcoholic liver disease	<ul style="list-style-type: none"> History of alcohol abuse AST/ALT ratio often >2:1 AST and ALT both <500 IU/mL (if no other injurious processes; if >1000, evaluate for acetaminophen ingestion) GGT may be ↑
Chronic hepatitis C	<ul style="list-style-type: none"> Anti-HCV (HCV Ab) + HCV RNA + AST,ALT may be ↑ or normal
Chronic hepatitis B	<ul style="list-style-type: none"> HBsAg + (in some cases may be –) HBV DNA + (usually; may be undetectable in patients who take ARVs with activity against HBV, such as tenofovir, lamivudine, emtricitabine) HBeAg may be + or – AST,ALT usually ↑; may be normal
Primary biliary cholangitis	<ul style="list-style-type: none"> Anti-mitochondrial antibodies + Elevated Alkaline phosphatase +/- bilirubin Elevated IgM

Disease	Typical Findings (may not be present)
Primary sclerosing cholangitis	<ul style="list-style-type: none"> • History of inflammatory bowel disease • Elevated Alkaline phosphatase +/- bilirubin • Anti-nuclear antibody (ANA) often + • Anti-smooth muscle antibody (ASMA) often +
Autoimmune hepatitis	<ul style="list-style-type: none"> • ANA often + • ASMA often + • Anti-Liver kidney microsomal type (LKM-I) often + • Hypergammaglobulinemia (IgG)
Non-alcoholic Steatohepatitis (NASH)/Nonalcoholic fatty liver disease (NAFLD)	<ul style="list-style-type: none"> • History of metabolic syndrome (obesity, dyslipidemia, diabetes mellitus) • ↑ AST and/or ALT • Fatty infiltration of liver on imaging

Abbreviations: ANA = antinuclear antibodies; ASMA = antismooth muscle antibodies; GGT = gamma-glutamyltransferase; LKM = liver/kidney microsomes

Virologic Features of Liver Disease

HBV Diagnostic Tests and Interpretation

	Acute Hepatitis B	Recovery from Acute Hepatitis B	Chronic HBeAg+ Disease	Chronic HBeAg- Disease	Successful Vaccination	Recovery from Acute Hepatitis B with Loss of HBsAb
HBsAg	+	-	+	+	-	-
Anti-HBs	-	+	-	-	+	-
Anti-HBc IgM	+	-	-	-	-	-
	(may be only marker during window period)					
Anti-HBc	+	+	+	+	-	+
						(also termed "isolated HBcAb+")
HBsAg	+	-	+	-	-	-
Anti-HBe	-	+	-	+	-	+
		(in some cases)				(in some cases)
DNA (PCR if required)	+	-	+	+	-	-

HCV Diagnostic Tests and Interpretation

	Acute Hepatitis C	Spontaneously Resolved or Successfully Treated Hepatitis C	Chronic Hepatitis C	Low-Level Chronic Hepatitis C	False-Positive Hepatitis C
Anti-HCV	- or +	+	+	+	+
HCV RIBA	- or +	+	+	+	-
HCV RNA Quantitative	+	-	+	-	-
HCV RNA Qualitative	+	-	+	+	-
	(may be only marker during window period)				
HCV Genotype	+	-	+	+ or -	-

Cirrhosis

Definitions:

Compensated cirrhosis: Cirrhosis is present but without specific clinical complication of cirrhosis.

Decompensated cirrhosis: Patient with at least 1 complication of cirrhosis, such as ascites, jaundice, encephalopathy, or variceal hemorrhage.

Signs/Symptoms of Cirrhotic Decompensation	Causes
Upper GI bleeding	Variceal hemorrhage, portal hypertensive gastropathy
Confusion	Encephalopathy
Abdominal distention	Ascites
Edema	Hypoalbuminemia
Jaundice	Hyperbilirubinemia (liver insufficiency)
Dyspnea	Pleural effusion (hydrothorax), hepatopulmonary syndrome, porto-pulmonary syndrome

Diagnostic Tests for Cirrhosis

Liver biopsy (“gold standard”): histological diagnosis made by liver biopsy or at autopsy. Especially useful in patients with discordant findings on different tests.

Alternatives to liver biopsy:

The invasive nature of biopsy and intrinsic limitations from sampling error and observer variability have led to the use of noninvasive methods, including serum markers and transient elastography (TE). Tests based on serum markers include the FIB-4 scoring system (uses age, platelet count, AST and ALT; online calculator: <https://www.hepatitisc.uw.edu/page/clinical-calculators/fib-4>) and the AST to Platelet Ratio Index (APRI) (online calculator: <https://www.hepatitisc.uw.edu/page/clinical-calculators/apri>).

Transient elastography is an ultrasound technique that measures liver stiffness, which correlates to fibrosis.

Diagnosis may be made radiologically in combination with above tests.

Potential Laboratory Findings in Patients with Cirrhosis

Indicators of Liver Insufficiency:

↑ Bilirubin

↑ Prothrombin time or INR

↓ Albumin

Indicators of Portal Hypertension:

- ↓ Platelets (earliest finding)
- ↓ Leukocytes and neutrophils
- ↑ Globulins

Role of Abdominal Imaging in Liver Disease

- Radiological findings that suggest the presence of cirrhosis include:
 - Small, contracted liver
 - Surface nodularity, increased echogenicity of liver
 - Splenomegaly
 - Ascites
 - Collateral veins (the most important finding indicative of cirrhosis)
 - See **Management of Complications of Cirrhosis and Chronic Liver Disease: Detection, Prevention, Treatment** below.
- The major use of abdominal imaging is for detecting complications of cirrhosis (e.g., ascites, hepatocellular carcinoma, and hepatic or portal vein thrombosis) in cirrhotic patients.
- In patients with chronic liver disease but without cirrhosis, abdominal imaging can be completely normal or can show fatty liver, a nonspecific finding.
- Useful radiology studies include abdominal ultrasound, abdominal CT scan, and abdominal MRI.

Prediction of the Risk of Fibrosis, End-stage Liver Disease, Hepatic Decompensation, and Hepatocellular Carcinoma

For FIB-4 >3.25 (high degree of fibrosis), ESLD risk was 7.9% at 1 year to 26.0% at 5 years among non-blacks and 2.4% at 1 year to 14.0% at 5 years among blacks.

FIB-4 score is a better predictor of the risk of developing hepatic decompensation and hepatocellular carcinoma than CTP and MELD scores in patients who are HCV+, but has not been validated in HIV/HCV-co-infection. FIB-4 predicts the risk of hepatocellular carcinoma in patients infected with HIV.

Lower plasma zinc concentrations are associated with liver fibrosis progression and mitochondrial oxidative stress in patients co-infected with HIV and HIV/HCV.

In a large cohort of Veterans co-infected with HIV/HCV with ALT 40 IU/L or less, statin use was protective of cirrhosis; for every 30% increase in time on statin, there was a 32% decreased risk of developing cirrhosis. Diabetes and low HDL were associated with cirrhosis in patients with ALT >40 IU/L (hazard ratios 1.15 and 1.3, respectively).

In a large cohort of women co-infected with HIV/HCV, marijuana use was not associated with progression to liver fibrosis.

HIV/HBV/HCV triple infection is strongly associated with the risk for decompensation.

Liver stiffness, assessed by TE, is associated with the risk of decompensation in HIV/HCV co-infection.

Staging and Classification of Cirrhosis

Child-Turcotte-Pugh (CTP) Classification of Liver Disease

- Originally developed to estimate the risk of death after portacaval shunt surgery; it was later modified to assess the risk of non-shunt operations and is currently used for prognosis.
- The score is determined by assessing clinical (subjective) complications of cirrhosis and laboratory (objective) abnormalities indicative of liver dysfunction.

Child-Turcotte-Pugh Classification of Liver Disease

Points Assigned

Parameter	1	2	3
Ascites	Absent	Slight (or diuretic responsive)	Moderate/Tense (or refractory to diuretics)
Encephalopathy	None	Grade 1-2 (or precipitant induced)	Grade 3-4 (or chronic)
Bilirubin (mg/dL)	<2	2-3	>3
Albumin (mg/dL)	>3.5	2.8-3.5	<2.8
Prothrombin time (seconds over control) or INR	PT: 1-3 or INR: <1.7	PT: 4-6 or INR: 1.7-2.3	PT: >6 or INR: >2.3

Grade	Score	1-year survival	2-year survival
A	5-6	100	85
B	7-9	81	57
C	10-15	45	35

Model for End-Stage Liver Disease (MELD) Score

- The MELD score was developed to predict 3-month survival following transjugular intrahepatic portosystemic shunt (TIPS). In patients with cir-

rhosis, an increasing MELD score is associated with increasing severity of hepatic dysfunction. Since 2002, it has been used for liver allocation (prioritization of patients awaiting transplantation) by the United Network for Organ Sharing (UNOS) and has been adopted for the non-transplant setting.

- It is the strongest predictor of mortality in patients infected with HIV with ESLD.
 - Expressed on a numerical scale, ranging from 6 to 40
 - Computed using bilirubin, INR, and Creatinine clearance

MELD = $3.78[\text{Ln serum bilirubin (mg/dL)}] + 11.2[\text{Ln INR}] + 9.57[\text{Ln serum creatinine (mg/dL)}] + 6.43$

- Hyponatremia is a common problem in patients with advanced cirrhosis, and the severity of the hyponatremia is a marker of the severity of the cirrhosis. In 2016, the MELD score was updated to include serum sodium as a factor in the calculation of the MELD (MELDNa).
- A calculator for determining MELD scores is available on the Mayo Clinic website, <https://optn.transplant.hrsa.gov/resources/allocation-calculators/meld-calculator/>.
- Hepatocellular carcinoma (HCC) and other complications of cirrhosis are ascribed additional MELD points.

Rx MANAGEMENT

Goals: prevention of further liver damage, slowing progression of liver disease, management of cirrhotic complications

Cirrhosis Quicknotes - <https://www.hepatitis.va.gov/provider/guidelines/cirrhosis-quicknotes.asp>

Prevention of further insults to the liver:

- HAV vaccination
- HBV vaccination
- Pneumococcal vaccination
- Influenza vaccination
- Avoid or minimize alcohol intake and hepatotoxic drugs
- Maintain normal BMI (avoid obesity)
- For hepatically-metabolized drugs, adjust dosages according to package insert instructions

Slow progression of liver disease:

- Abstinence from alcohol use for all, regardless of underlying disease process: counsel or refer for treatment, as appropriate. See **Alcohol Use**, p. 91.

- Avoidance of hepatotoxic or nephrotoxic medications (e.g., NVP, ddl, NSAIDs, aminoglycosides)
- Treatment of HIV, if co-infected with HBV or HCV; ARV therapy may slow progression of HBV and HCV
- Treatment of chronic HCV, if eligible: with direct-acting anti-virals +/- ribavirin
- Treatment of chronic HBV, if eligible: currently FDA-approved medications for treatment of HBV include lamivudine (3TC), tenofovir disoproxil fumarate (TDF), entecavir, adefovir, and pegylated interferon-alfa. Another ARV, emtricitabine (FTC) is also active against HBV, but is not approved for treatment of HBV.
 - HBV suppression reduces the risk of hepatic decompensation and HCC; HBV should be treated regardless of stage of fibrosis due to increased risk for hepatocellular carcinoma.
 - It is very important to note that, when using HBV antiviral agents that are also active against HIV (e.g., 3TC, FTC, TDF, or entecavir) in a patient co-infected with HIV and HBV, these agents should not be used as monotherapy. In co-infected patients, the HBV medications must be used as combination therapy within a fully suppressive HIV regimen to avoid development of HIV resistance.
- Treatment of autoimmune hepatitis: can include prednisone or immunosuppressive agents

Management of Complications of Cirrhosis and Chronic Liver Disease: Detection, Prevention, Treatment

Note: Patients with cirrhosis are best managed in collaboration with a GI specialist, particularly those with severe or recurrent complications, based on the 2012 VA Hepatitis C Resource Center recommendations on management and treatment of cirrhosis. A summary of these recommendations can be found at <http://www.hepatitis.va.gov/pdf/2012HCV-guidelines.pdf>.

Ascites

Overview:

- Cirrhosis accounts for 85% of the cases of ascites. Ascites is the most common complication of cirrhosis.
- 30% of patients with compensated cirrhosis develop ascites within 5 years, 58% will develop in 10 years.
- 2-year survival rate of patients with ascites is 50%.

Primary prophylaxis:

- Treat underlying liver disease
- Discontinue alcohol

- Low-salt diet (1-2 g Na/day); may liberalize salt intake if salt restriction results in poor food intake
- Fluid restriction is not necessary unless serum sodium is less than 125 mmol/L.

Treatment: Diuretics (e.g., spironolactone alone or together with furosemide)

- Start with spironolactone 50-100 mg and furosemide 20-40 mg daily and sequentially increase as necessary and tolerated to maximum dosage of spironolactone 400 mg daily and furosemide 160 mg daily. Can start with spironolactone alone if there is severe hypokalemia.
- Avoid concomitant use of ACE inhibitors and NSAIDs because of risk of hepatorenal syndrome.
- Patients with massive ascites may require therapeutic large-volume paracenteses, often with albumin supplementation; should be treated in consultation with a GI/hepatology specialist.
- Refractory ascites may require placement of a TIPS.

Spontaneous Bacterial Peritonitis (SBP)

Overview:

- Bacterial infection of ascitic fluid in the absence of an intra-abdominal source of infection.
- Diagnosis: Polymorphonuclear leukocyte (PMN) count of >250 cells/ μ L in the ascitic fluid, culture results are positive, and secondary causes of peritonitis are excluded. Sample is usually obtained via paracentesis.
- Patients may be asymptomatic, may have subtle clinical findings, or may have fever, abdominal pain, hypotension, or altered mental status.

Primary prophylaxis: Antibiotic prophylaxis decreases risk of bacterial infection and mortality. It is recommended in patient with the following risk factors: previous episode of SBP, admitted patients who have ascitic fluid protein concentration <1 g/dL, gastrointestinal bleeding. Regimens include trimethoprim-sulfamethoxazole (one double-strength tablet once daily) or fluoroquinolone therapy (ciprofloxacin 500 mg/day). Length of treatment depends on risk factor (GI bleeding, up to 7 days; low protein concentration, during admission; previous episode SBP, lifelong).

Treatment:

- Third-generation cephalosporin, ampicillin/sulbactam, or fluoroquinolone, given IV for initial occurrence; avoid aminoglycosides
- Discontinue beta-blockers

Variceal Hemorrhage/GI Bleeding

Overview:

- ~25% of patients with cirrhosis and varices experience hemorrhage from gastroesophageal varices in the first year after diagnosis.
- The bleeding-related mortality is around 30%.

Screening: Upper endoscopy (EGD) is recommended for every patient with cirrhosis to screen for esophageal varices or to investigate the etiology of bleeding.

Primary prophylaxis refers to the prevention of a first episode of variceal hemorrhage. Nonselective beta-blockers (propranolol or nadolol) or endoscopic variceal ligation (EVL) are recommended for prophylaxis in patients with advanced cirrhosis (CTP B or C), high risk stigmata (red wale sign (red streak on an esophageal varix)) or large varices.

- Recommendation: Propranolol; start 10-20 mg PO BID, increase as tolerated (goal is to titrate to a heart rate of 50-60 bpm, if tolerable). Nadolol can be given once daily, starting at 40 mg per day.
- Starting beta-blockers is not recommended unless varices have been documented.
- Stop beta blockers in patients with SBP or recurrent ascites.

Treatment: When a variceal bleed occurs, immediate hospitalization and GI consultation are needed for treatment.

Secondary prophylaxis: After a variceal bleed, the combination of nonselective beta-blockers and endoscopic variceal ligation are recommended to decrease the risk of another bleed.

Hepatic Encephalopathy

- Variable abnormalities of neurological and psychiatric function, including insomnia, hypersomnia, irritability, confusion, disorientation, hyperactive deep tendon reflexes, and asterixis.
- Diagnosis: Based on clinical picture rather than laboratory or imaging results. Ammonia level usually elevated.

Primary prophylaxis: None

Treatment: Mainly consists of identification and treatment of precipitating factors;

- It is essential to correct hypokalemia.
- Lactulose: start at 30-40 mL (20-30 g) PO every 1-2 hours until bowel evacuation, then, two to four times per day titrated to achieve 2 to 3 soft stools per day. Avoid diarrhea as it will lead to volume depletion and dehydration.
- Rifaximin: 400 mg PO TID (or 550 mg BID) is an alternative for patients who cannot tolerate lactulose, or in combination with lactulose in patients with refractory symptoms on lactulose alone.

Secondary prophylaxis: None; once precipitating factors are eliminated, lactulose can be discontinued; in patients with recurrent encephalopathy, chronic treatment with Lactulose + /- Rifaximin is warranted.

- Sedatives and tranquilizers should not be used.
- Excessive diuresis and constipation should be avoided.

Hepatocellular Carcinoma (HCC)

- Incidence varies widely according to geographic location, as well as among various ethnic groups within the same country.
- In the United States, the incidence of HCC is rising and has almost doubled during the past 2-3 decades, chiefly among patients with cirrhosis secondary to HCV; in the VA, the number of HCC cases nearly doubled between 2004 and 2007.
- A study of 384 patients with HCV and compensated cirrhosis found that 1.4% per year developed HCC. A low CD4 count is also a risk factor for development of HCC, hence ARV therapy is recommended in all patients infected with HIV, regardless of CD4 count.
- 20-56% of patients who develop HCC have previously undiagnosed cirrhosis.
- In chronic HBV, HCC can occur before the development of cirrhosis, but in other chronic liver diseases, HCC typically does not occur until there is cirrhosis.

Risk factors:

- Age
- Duration of liver disease
- Male sex
- HBV (can occur in patients with or without cirrhosis, with inactive, carrier HBV [HBsAg+, normal ALT, undetectable or low-level HBV DNA], and in those with chronic HBV [HBsAg+, elevated ALT, high HBV DNA])
- Chronic HCV with cirrhosis
- Hereditary hemochromatosis with cirrhosis, alcoholic cirrhosis
- Cirrhosis of almost any other cause

Treatment: Potential indication for liver transplant; other treatment options include tumor resection, radiofrequency tumor ablation, transarterial chemoembolization, or chemotherapy; refer to Hepatology or Oncology.



Screening for Hepatocellular Carcinoma

Based on American Association for the Study of Liver Diseases [AASLD] guidelines for management of HCC available at <http://www.aasld.org/publications/practice-guidelines-0>.

Patients who should be screened for HCC:

Note: some patients with chronic HBV are at increased risk even in the absence of cirrhosis.

- HBsAg+ Asian males 40 years of age
- HBsAg+ Asian females 50 years of age
- HBsAg+ and cirrhosis
- HBsAg+ African/North American blacks
- HBsAg+ with a family history of HCC
- Cirrhosis resulting from alcohol use
- Cirrhosis resulting from HCV
- Cirrhosis resulting from genetic hemochromatosis, primary biliary cholangitis, alpha-1 antitrypsin deficiency
- Patients on transplant waiting list
- Other cirrhosis

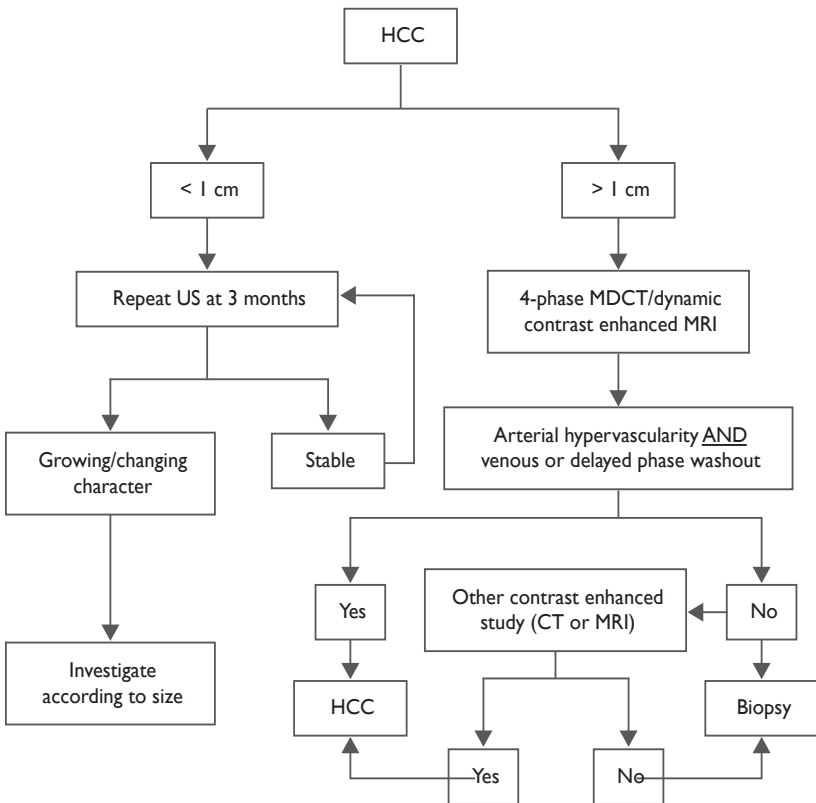
Recommended Technique and Time Intervals for HCC Screening

- Surveillance should be performed every 6 months using ultrasound. Because ultrasound is particularly operator dependent, some centers where ultrasound reliability is low may choose to use either contrast enhanced CT or MRI for surveillance imaging.
- Patients co-infected with cirrhosis and HIV/HCV, who achieve sustained virologic response, should still undergo regular surveillance.
- Alpha-fetoprotein (AFP) alone should not be used alone as a screening tool for HCC unless ultrasound is not available: it has poor sensitivity and specificity.
 - AFP measurement is recommended if a focal hepatic mass is detected with ultrasound or other abdominal imaging.
 - AFP level does not correlate well with other clinical features of HCC, such as size, stage, or prognosis.
 - Based on a systematic review, with a cutoff of 20 mcg/L, AFP has sensitivity of 41-65% and specificity of 80-94%.

How to Evaluate a Hepatic Mass Found on Screening Ultrasound

- For a mass <1 cm in diameter found on ultrasound in a cirrhotic liver: repeat ultrasound in 3-4 months to look for stability versus a change in size.
- For a mass >1 cm in diameter found on ultrasound in a cirrhotic liver: CT scan with 4-phase dynamic vascular imaging.
- For evaluation, see **Figure 1** below.

Figure 1: Algorithm for Investigation of Small Nodules Found on Screening in Patients at Risk of HCC (MDCT = multidetector CT Scan)



Liver Transplantation

Note: Current information on VA transplantation policy and procedures can be found at the website for the VA National Transplant Program at <https://www.va.gov/transplant>. New resources for providers can be found at <https://www.hepatitis.va.gov/products/#P4X>.



BACKGROUND

- Chronic hepatitis C with progression to ESLD or HCC is the most common reason for liver transplantation, both within the VA system and in the United States general patient population.
- VA patients may be referred for liver transplantation within the VA system or at affiliated academic medical centers.
- Currently, approximately 100 liver transplants are performed annually within the VA system, with survival rates that meet or exceed UNOS averages.
- Patients infected with HIV are eligible for consideration for liver transplantation at selected VA transplant centers.
- Referral for liver transplantation involves submission of a transplantation package to the VA Central Office; if approved, the package is forwarded to one of the national VA liver transplant centers for further evaluation.
- For transplant candidates infected with HIV, the application package must contain an infectious disease evaluation using a template specified by the VA National Transplant Program.
- In cases of fulminant hepatic failure or other critical situations, emergency applications may be made by contacting the VA National Transplant Program.

Transplant Referral

- The local VA Medical Center Transplant Referral Coordinator should be consulted as soon as referral for liver transplantation is under consideration.
- Update Child-Turcotte-Pugh and MELD scores regularly. For purposes of ESLD follow-up, patients should be seen as follows based on MELD scores (note: other factors may indicate more frequent follow-up):
 - ≤ 10 : at least every 6-12 months
 - 11-18: at least every 3 months
 - 19-24: at least every month
 - ≥ 25 : at least every week
- Refer for transplant evaluation if:
 - Child-Turcotte-Pugh score is ≥ 7 or MELD score is ≥ 15

- MELD score is 11-13 and patient has refractory ascites or hyponatremia
- Meets HCC criteria for transplantation (≤ 3 masses, all ≤ 3 cm in diameter; WHO performance status < 3 ; Child-Turcotte-Pugh score ≤ 9)
- Patients must be abstinent from all substances, including tobacco. Active substance use of any kind, or < 6 months' sobriety, is the most common reason for rejection or deferral of patients for listing for transplantation; see **Alcohol Use**, p. 91; **Substance Use**, p. 107; and **Tobacco Use**, p. 127.
- Patients also must have documented adequate social support for care during the peritransplant and post-transplant periods.

Post-transplant Care

- Patients who have received liver transplants (whether inside or outside the VA system) will return to the referring VA Medical Center for care.
- 1-year survival rates are typically $> 80\%$.
- The major clinical issues in the post-transplant period are management of and toxicities from immunosuppressive agents required to prevent transplant rejection, drug interactions, and infectious complications of immunosuppression.
- See <https://www.hepatitis.va.gov/pdf/transplant-guide.pdf> for more information on post-transplant care.



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Coronary Artery Disease

KEY POINTS

Coronary arteries on the surface of the heart can become narrowed, hardened or ruptured when plaque builds up inside the arteries. It is one of a class of diseases called cardiovascular disease.



BACKGROUND

Cardiovascular disease (CVD) risk is increased by 40%–75% among adults infected with HIV compared with non-infected patients. CVD-related death is the second leading cause of non-AIDS fatalities in HIV patients. Veterans with HIV have a 50% increased risk of acute myocardial infarction compared to those without HIV. There is a higher risk of acute myocardial infarction among patients with HIV and a low recent or nadir CD4 cell count.

Risk Factors for Cardiovascular Disease in Patients with HIV

Traditional cardiovascular risk factors are more frequent in patients with HIV as compared with the general population: hypertension (HIV: 21.2 vs. non-HIV: 15.9%); diabetes (HIV: 11.5 vs. non-HIV: 6.6%); and dyslipidemia (HIV: 23.3 vs. non-HIV: 17.6 %). Patients are 2-3 times more likely to be smokers than their HIV-uninfected counterparts and have a high prevalence of metabolic syndrome (about 25%). Hypogonadism, also more common in men with HIV, is associated with increased cardiovascular risk.

Vitamin D deficiency contributes to coronary artery calcification in African Americans. Smoking, obesity, increased duration of antiretroviral therapy, HIV immune activation and inflammation, and kidney disease have also been reported as risk factors.

Mechanisms of Cardiovascular Disease in Patients with HIV

HIV infection promotes atherosclerosis by:

- induction of macrophage/monocyte activation
- production of proatherogenic sCD14 and CD163
- dysregulation of CD8 cells; the inversion of CD4:CD8 ratio in treated patients with HIV is associated with the progression of intimal media thickening

Note: Some medications mentioned in this chapter may not be available on the VHA National Formulary (<https://www.pbm.va.gov/NationalFormulary.asp>). Consult VA pharmacists for alternatives.

- increased levels of pro-inflammatory cytokines (C-reactive protein, interleukin-6)
- activation of the coagulation system

Immune activation in HIV infection is due to:

- intestinal bacterial translocation
- concurrent viral infections (cytomegalovirus, hepatitis B, hepatitis C, herpes simplex)
- residual HIV viremia or HIV proliferation in reservoir sites

Some HIV proteins, such as gp120, decrease nitric oxide levels in the endothelial cells, affecting vascular tone and platelet adhesion and aggregation.

CMV infection promotes atherosclerosis by producing pro-angiogenic factors such as IL-6 and granulocyte macrophage colony stimulating factor.

Hepatitis C co-infection is associated with a higher frequency of atherosclerotic plaques, stroke, and acute myocardial infarction when compared to non-HCV co-infected patients.

HIV-infected men with acute coronary syndrome have less arterial plaque than controls, indicating that plaque vulnerability is an important factor in the pathophysiology of myocardial infarction in patients with HIV infection.



EVALUATION

Several algorithms have been devised to calculate cardiovascular risk and determine the suitability of statin use. The Framingham algorithm determines the ten-year risk of cardiovascular disease using age, diabetes, smoking status, treated and untreated systolic blood pressure, total cholesterol, and HDL cholesterol.

For a calculator, see <https://www.mdcalc.com/framingham-coronary-heart-disease-risk-score>. If the 10-year risk is 20% or more, a statin is recommended. For patients over age 50 years old, low dose aspirin is also endorsed. For diabetic patients, a statin and aspirin are both indicated.

From the Framingham data, smoking cessation is the most important intervention because it decreases the risk of ischemic heart disease by about 50%. A 10mm Hg reduction in systolic blood pressure, a reduction of 39mg/dL in total cholesterol, and the use of aspirin each reduce the risk of ischemic heart disease by 20% to 25%, with these effects being additive.

The 2013 American Heart Association guidelines use the Pooled Cohort Equation (PCE) to calculate a 10-year cardiovascular disease risk, based on gender, age, race, total cholesterol, HDL cholesterol, systolic blood pressure, smoking, and diabetes. For a calculator, see <http://clincalc.com/cardiology/ascvd/pooledcohort.aspx>. The American Heart Association guidelines recommend use of moderate- to high-dose statins for asymptomatic adults 40 to 75 years old without a history of CVD who have an LDL-C concentration of 190 mg/dL or

greater, diabetes, or an estimated 10-year CVD event risk of 7.5% or greater, as calculated with the PCE risk calculator.

However, some investigations have concluded that patients with HIV have cardiovascular risk in excess of that predicted by the Framingham and Pooled Cohort equations, indicating that some component of cardiovascular risk is imparted by HIV infection itself.

To assess the validity of the Framingham Risk Score in the HIV population, 27 virologically-controlled patients with HIV and without known cardiac disease were evaluated for aortic wall inflammation using positron emission tomography. Compared with non-HIV controls matched for Framingham Risk Score, the patients with had higher levels of arterial wall inflammation. Thus, patients with HIV have additional cardiovascular risk, beyond that estimated by traditional risk factors. Another study used computer tomography angiography to determine how the PCE would perform for patients with HIV. One hundred eight patients with HIV and without known CVD had angiography and coronary artery plaque morphology was classified as with or without high-risk characteristics. Thirty-nine subjects had high-risk plaque morphology, but statin therapy would not have been recommended for 74% of these by the PCE. Thus, once again, it appears current cardiovascular risk equations underestimate risk in patients with HIV.

Thus, new models of risk prediction specific for the HIV population have been devised. The Data Collection on Adverse Effects of Anti-HIV Drugs (D:A:D) study equation uses age, sex, systolic blood pressure, serum cholesterol and HDL-cholesterol levels, diabetes, smoking status, family history of CVD, current use of abacavir, indinavir, or lopinavir; and the number of years on indinavir or lopinavir as the variables. The D:A:D risk model was based upon data obtained from the large cohort of patients with HIV followed longitudinally for cardiac events. For a calculator, see <http://www.chip.dk/Tools>. The D:A:D calculator arrives at a 5-year risk for a composite CVD outcome of myocardial infarction, stroke, invasive cardiac/vascular procedure, or death. In this cohort, increased levels of C-reactive protein, uncontrolled HIV viral load at time of the cardiovascular (CV) event, and slower immune reconstitution were also linked with increased cardiovascular risk.

In one study, the Pooled Cohort Equation (PCE), Framingham (FRS), and D:A:D risk scores were compared in their prediction of cardiovascular events in a cohort of 2550 HIV patients followed for 17,337 patient-years. The three algorithms performed equally well for the prediction of events. However, the PCE or D:A:D algorithms more accurately identified patients at low risk for cardiovascular events. With the lack of superiority of any of the three algorithms, it is necessary to develop new algorithms that incorporate additional variables, such as immunologic or virologic status, to accurately assess cardiovascular risk in HIV patients. A critique of the D:A:D study is that the follow-up period is relatively short.

Another study used computed tomography angiography to determine how the PCE would perform in patients with HIV. One hundred eight HIV-infected

patients without known CVD had angiography and coronary artery plaque morphology was classified as with or without high-risk characteristics. Thirty-nine subjects had high-risk plaque morphology, but statin therapy would not have been recommended for 74% of these by the PCE. Thus, once again, it appears current cardiovascular risk equations underestimate risk in patients with HIV. One problem with applying cardiovascular risk equations formulated for the general population to patients with HIV are differences in the mechanism of myocardial infarction. Type 1 MIs result from instability of atherosclerotic plaques, whereas type 2 MIs are due to a mismatch between oxygen demand and supply, as in sepsis, vasospasm from cocaine or amphetamines, severe anemia, and volume fluctuations. In the general population, 25% of MIs are type 2, whereas in patients with HIV these represent about half of all MIs.

Thus, in the absence of specific guidelines for use in patients with HIV, it is recommended that HIV clinicians continue to use the original National Cholesterol Educational Program (NCEP) guidelines. See **Table 1** below.

HIV Infection and Microvascular Disease

HIV infection increases the risk of microvascular disease. Among HIV patients with suppressed viremia on antiretroviral therapy, the total CD8 count, the frequency of CD8 cells expressing activation marker PD-1 and levels of D-dimer, high-sensitivity C-reactive protein, sCD-14, interleukin-6, and tumor necrosis factor-alpha were all associated with increased microvascular disease, as measured by reactive hyperemia in the brachial artery.

Other Heart Conditions in Patients with HIV

Patients with HIV have higher rates of sudden arrhythmic death and prolonged QT-interval, a major risk for polymorphous ventricular tachycardia (Torsades de pointes). Sudden cardiac death rate (due to ischemic and/or arrhythmic causes) is 4.5-fold higher in patients with HIV as compared to the general population. Patients with HIV have a reduction in cardiac autonomic function with a shift toward sympathetic dominance which predisposes them to an elevated risk of arrhythmias and cardiac events.

Patients with HIV have an increased risk of heart failure, systolic and diastolic dysfunction, and myocardial fibrosis and steatosis. Compared with uninfected Veterans, Veterans with HIV have an increased risk of heart failure with preserved ejection fraction (HFpEF) (hazard ratio [HR], 1.21), borderline HFpEF (HR 1.37), and heart failure with reduced ejection fraction (HFrEF; HR 1.61). The risk of HFrEF was particularly evident in Veterans <40 years old (HR 3.59). An HIV-1 viral load of ≥ 500 copies/mL compared with < 500 copies/mL was associated with an increased risk of HFrEF, and CD4 cell count < 200 cells/mm³ compared with ≥ 500 cells/mm³ was associated with increased risks of HFrEF and HFpEF. There are also higher rates of atrial fibrillation and pulmonary hypertension in

patients with HIV. Chronic inflammation likely plays an etiologic role in these conditions.



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Dermatologic Conditions

This chapter will focus on the diagnosis and treatment of some of the most common dermatological diseases in adults with HIV infection: seborrheic dermatitis, folliculitis, onychomycosis, psoriasis, and HPV-associated warts.

KEY POINTS

- Immunologic status strongly influences the incidence and clinical presentation of many dermatologic conditions.
- At CD4 counts of <50 cells/ μ L, patterns in skin findings can become atypical.
- In the absence of effective antiretroviral (ARV) therapy, up to 40% of patients with HIV infection and 80% of those with AIDS have seborrheic dermatitis; this condition usually improves with ARV therapy.
- Eosinophilic folliculitis is seen more commonly in patients with CD4 counts of <200 cells/ μ L, and during immune reconstitution. It usually improves after 6 months on ARV therapy.
- Staphylococcal folliculitis is the most common dermatologic conditions in patients with HIV. It is more common in patients with CD4 counts of <200 cells/ μ L. Presumptive treatment should include coverage for methicillin-resistant *Staphylococcus aureus* (MRSA).
- Onychomycosis should be confirmed by potassium hydroxide (KOH) preparations of nail clippings before treatment. Onychomycosis has an incidence of 20–44% and is more commonly seen with CD4 counts ≤ 450 cells/ μ L. Oral antifungals interact with many ARVs; consult dosing information before prescribing.
- Psoriasis can be severe ($>50\%$ of the body surface area) in patients with CD4 counts of <200 cells/ μ L, particularly those not on effective ARV therapy.
- HPV-associated warts are difficult to treat, require multiple treatments, and may recur despite ARV therapy.



BACKGROUND

Epidemiology

- Dermatological diseases are common among persons with HIV infection.
- In one large population study, 69% of patients with HIV infection had cutaneous disease.
- Seborrheic dermatitis is a very common dermatologic diagnosis.
- At CD4 counts of <50 cells/ μ L, patterns in skin findings can be atypical.
- Skin findings may represent opportunistic infections or other illnesses
- Certain ARV therapies are more likely to cause rash: nevirapine, efavirenz, abacavir (rechallenge).

Note: Some medications mentioned in this chapter may not be available on the VHA National Formulary (<https://www.pbm.va.gov/NationalFormulary.asp>). Consult VA pharmacists for alternatives.

Skin Conditions Frequently Observed in Patients with HIV Infection

- **AIDS-defining conditions**
 - Ulcerating herpes simplex virus infection (duration >1 month)
 - Kaposi sarcoma
 - Cryptococcosis of the skin (usually in the context of disseminated infection)
 - Histoplasmosis of the skin (usually in the context of disseminated infection)
 - Coccidioidomycosis of the skin (usually in the context of disseminated infection)
 - Cytomegalovirus
- **Non-AIDS-defining conditions indicative of HIV-associated immunodeficiency**
 - Herpes zoster infection exceeding one dermatome or disseminated
 - Bacillary angiomatosis
 - Molluscum contagiosum—extensive or large lesions in adults
 - Eosinophilic folliculitis
 - Papular pruritic eruptions of HIV
- **Other conditions frequently found in patients with HIV Infection**
 - Seborrheic dermatitis
 - Xerosis cutis
 - Proximal subungual onychomycosis
 - Crusted scabies
 - Anal intraepithelial neoplasia
- **Pruritus**
 - 45% of patients with HIV complain of itching, associated with dermatologic conditions, systemic conditions, neuropathy, and psychiatric conditions.
 - Half of itching patients reported negative quality of life impact.
- **Pruritus Associated with Dermatologic Conditions**
 - Atopic eczema
 - Contact dermatitis
 - Eosinophilic folliculitis
 - Insect bites
 - Lichen planus
 - Lichen simplex chronicus

- Prurigo nodularis
- Pruritic papular eruption of HIV
- Psoriasis
- Scabies
- Xerosis
- **Pruritus Associated with Non-dermatologic Causes**
 - Systemic:
 - Cholestasis
 - Chronic kidney disease
 - Hyperthyroidism
 - Polycythemia vera
 - Hodgkin Lymphoma
 - Neuropathic:
 - Brachioradial pruritus
 - Notalgia paresthetica
 - Postherpetic neuralgia
 - Psychogenic/psychiatric:
 - Delusions of parasitosis
 - Obsessive-compulsive disorder
 - Substance abuse
- **Therapeutic approach to pruritus**
 - Histamine is not the only mediator of itching, so antihistamines may not be uniformly beneficial.
 - Topical treatments include calamine, pramoxine-containing creams, and corticosteroids.
 - For neuropathic itching, gabapentin and pregabalin may be beneficial.
 - For cholestatic and psychogenic itching, antidepressants such as mirtazapine, paroxetine, and sertraline may be helpful.
 - For xerosis, moisturizers are beneficial. Prurigo nodularis and lichen simplex chronicus are associated with severe itching.

Dermatologic Conditions According to Clinical Status

Clinical Status	Associated Dermatological Diseases
Most common at CD4 counts of <200 cells/μL in patients not on effective ARV therapy <200 cells/μL in patients who are not on effective ARV therapy	<ul style="list-style-type: none"> • Severe psoriasis (>50% body surface area) • Extreme photodermatitis • Prurigo nodularis • Molluscum contagiosum. See photo at end of chapter. • Adverse drug reactions • Mycobacteria: <i>M. tuberculosis</i>, <i>M. kansasii</i>, MAC • Fungal infections (e.g., <i>Cryptococcus</i>, <i>Aspergillus</i>) • Herpes zoster • Eosinophilic folliculitis • Bacillary angiomatosis (<i>Bartonella spp.</i>) • Kaposi sarcoma • Lichenification • Diffuse seborrheic dermatitis

EVALUATION AND MANAGEMENT

Seborrheic Dermatitis*

Etiology	Findings/ Distribution	Diagnostic Clues	Management
May be related to skin-surface yeasts (<i>Malassezia furfur</i>) and environmental factors.	<p>Erythematous scaly plaques on the central face, scalp, behind ears</p> <p>Can be pruritic.</p> <p>Can affect sternum, axillae, and genital region.</p>	<p>More severe, atypical, and diffuse in patients with low CD4 count nadirs</p> <p>Common in patients who are not on ARV therapy: up to 40% of patients with HIV infection and 80% of AIDS patients have seborrheic dermatitis.</p> <p>Should improve with ARV therapy.</p>	<p>Hydrocortisone 1% ointment mixed with ketoconazole 2%, clotrimazole 1%, or econazole 2% applied BID to affected area</p> <p>If very itchy: triamcinolone 0.5% ointment in non-facial areas</p> <p>Scalp: ketoconazole 2%, coal tar 1%, selenium sulfide 2%, or zinc pyrithione 2% Sshampoo twice weekly; leave lather</p>

Etiology	Findings/ Distribution	Diagnostic Clues	Management
-	-	-	on for 5 minutes before rinsing For recalcitrant cases: fluconazole 200 mg PO daily for 1 week

* See photo at end of chapter.

Folliculitis

Etiology	Findings/ Distribution	Diagnostic Clues	Management
Eosinophilic folliculitis. See photo at end of chapter.	Numerous, extremely itchy pustules on the face, neck, scalp, and trunk	<p>Mainly seen in patients with CD4 counts of <300 cells/μL.</p> <p>Can be seen during immune recovery after ARV therapy in the first 3-6 months on ARV therapy.</p> <p>Very pruritic, especially on face.</p>	<p>ARV therapy often results in resolution of eosinophilic folliculitis as CD4 cell counts increases above 250 cells/μL.</p> <p>Topical corticosteroids e.g., desonide 0.05% cream for the face and triamcinolone 0.1% ointment for the body.</p> <p>Indomethacin (50-75 mg a day)</p> <p>cetirizine (20-40 mg a day)</p> <p>Refractory eosinophilic folliculitis is beyond topical steroids, ARV and antihistamines and should be referred to Derm for Bx confirmation and discussion of systemic Tx. May be beyond the scope of PCP guidelines.</p>
<i>Pityrosporum</i> folliculitis. See photo at end of chapter.	Erythematous papules and tiny pustules along hair follicles	Looks like a milder version of bacterial folliculitis with much smaller lesions.	Both topical and oral antifungals are effective.

Etiology	Findings/ Distribution	Diagnostic Clues	Management
-	-	<p>Lesions are smaller and less pruritic than eosinophilic folliculitis.</p> <p>Commonly excoriated.</p> <p>Less likely to form large pustules.</p> <p>Overgrowth of tinea</p>	-
Staphylococcus folliculitis	Erythematous papules and pustules along hair follicles	<p>Most common skin finding in HIV</p> <p>Often excoriated.</p> <p>Often draining pus</p> <p>Presents as an erythematous flare.</p> <p>MRSA common; consider culture to guide treatment.</p>	<p>If localized, consider topical mupirocin 2% ointment or topical clindamycin 1% solution.</p> <p>Presumptive treatment for MRSA infections:</p> <ul style="list-style-type: none"> • TMP-SMX DS BID, or doxycycline 100 mg BID, treat for 10-14 days • If severe, IV vancomycin or oral linezolid per hospital protocol • Nares should be treated with intranasal mupirocin QHS for 5 days. <p>If confirmed MSSA: dicloxacillin or cephalexin</p> <p>Consider dilute bleach baths or topical chlorhexidine.</p>
Pseudomonal folliculitis	Papular lesions appear within 8-48 hours after exposure.	Associated with use of hot tub and wet suit/swimwear (lesions may be concentrated in areas covered by swimwear).	For immunosuppressed persons or those with prolonged or severe cases, consider treating with ciprofloxacin 500mg BID for 10 days.

Etiology	Findings/ Distribution	Diagnostic Clues	Management
-	-	In immunocompetent persons, self-limited to 7-14 days	-

*See **Potential ARV Interactions**, below.

Be sure to differentiate folliculitis and acne.

- Acne presents with red papules and pustules on face, neck, arms, and back.
- Acne can be associated with exogenous testosterone, estrogens, anabolic steroids, corticosteroids, isoniazid, lithium, anti-convulsants (phenytoin, carbamazepine), and psychotropic medications (trazodone, haloperidol, aripiprazole), as well as immune reconstitution inflammatory syndrome.
- Management: Stop the offending drug, if possible.
- Treat cystic acne with doxycycline or minocycline. If severe and unresponsive to antibiotics, consider dermatology referral for the consideration of oral isotretinoin. Because of its toxicity and teratogenicity, isotretinoin use is restricted in the United States. See the VA Pharmacy Benefits Management Services website for more information, <http://www.pbm.va.gov/clinicalguidance/criteriaforuse.asp>.

Onychomycosis

- Refers to invasion of nails by dermatophytes (tinea unguium; with 3 subtypes), yeast, or molds.
- Dermatophytes account for 90% of the cases of onychomycosis of the toenails and <50% of fingernail infections.
- Onychomycosis is widespread in the general population and is responsible for significant morbidity and complications that must be treated.
- Increased prevalence among patients with HIV infection, with more severe disease if CD4 count is <400 cells/ μ L.
- Thought to be the cause of 50-60% of abnormal-looking nails.
- Differential diagnosis includes psoriasis, eczematous conditions, onychogryphosis/neglect, trauma, and lichen planus.
- Poor response to treatment: Before starting treatment, inform patients about long duration of treatment, high rates of treatment failure (25-50%) and recurrence (20-50%).
- Emerging treatments to watch are: efinaconazole, ravuconazole, and long-pulsed 1064-nm Nd:YAG laser therapy.

Type	Findings/ Distribution	Diagnostic Clues	Management
<p>Distal subungual onychomycosis See photo at end of chapter.</p> <p>Infection with <i>Trichophyton rubrum</i> in vast majority of cases</p>	<p>Affects great toe first; can affect all toes.</p> <p>Begins with discoloration of distal corner of nail, spreads across nail, then extends toward cuticle.</p> <p>Distal nail plate can break off, becoming heaped and irregular.</p>	<p>Nail clipping culture: gold standard</p> <p>KOH preparation: clip or file nail-plate and collect scales from most proximal area.</p> <p>Look for hyphae and arthrospores.</p> <p>Lower sensitivity; may need >2 preparations.</p> <p>If KOH negative, consider nail clipping for histopathology / PAS stain.</p>	<p>Indications for treatment: cellulitis, pain, patient desire for treatment</p> <p>Oral therapies* (in order of decreasing efficacy):</p> <ul style="list-style-type: none"> • Terbinafine 250 mg daily • Itraconazole 400 mg daily for 1 week each month • Fluconazole 150 mg once weekly <p>Treat fingernails for 6 weeks, toenails for 12 weeks</p> <p>Fluconazole 400 mg once weekly for 6 months has shown efficacy in immunocompromised patients; fluconazole has fewer drug interactions than itraconazole.</p> <p>Terbinafine and itraconazole have higher cure rates than other forms of therapy, are generally well tolerated. Recurrences of the infection are frequent.</p> <p>Topical therapies generally ineffective; topical ciclopirox nail lacquer can be used with patients who cannot safely take oral therapy; trials show 7% cure rate.</p> <p>Surgery: removal of nail plate in isolated nail infection or</p>

Type	Findings/ Distribution	Diagnostic Clues	Management
-	-	-	dermatophytoma. See Potential ARV Interactions , below, and Common Medications , p 11.
Proximal subungual onychomycosis <i>Trichophyton rubrum</i> most common. Marker of HIV infection, immunocompromised state.	Discoloration begins at cuticle and extends distally.	Same as above	Same as above
White superficial onychomycosis <i>Trichophyton mentagrophytes</i> most common	Starts as dull white spots, then spreads centrifugally.	White areas are soft and can be scraped with a curette for culture or KOH slide.	Same as above
Candida onychomycosis <i>Candida albicans</i> More common in patients with HIV infection	Common cause of fingernail infection Often in previously damaged nails Rarely in toenails Nail thickening and discoloration Can lead to onycholysis.	Fingernail scraping should be sent for culture of yeast.	Oral therapies (in order of decreasing efficacy), pulse dosing: <ul style="list-style-type: none"> • Itraconazole 200 mg QD for 1 week each month • Terbinafine 250 mg QD for 1 week each month Treat for 2 months (fingernails), 3 months (toenails)
Mold (e.g., <i>Aspergillus</i> , <i>Scopulariopsis</i>)	Rare cause of toenail infection	Consider when dermatophyte infection is ruled out	Oral therapies (in order of decreasing efficacy), pulse dosing: <ul style="list-style-type: none"> • Itraconazole 200 mg QD for 1 week each month

Type	Findings/ Distribution	Diagnostic Clues	Management
-	-	-	<ul style="list-style-type: none"> Terbinafine 250 mg QD for 1 week each month Treat 2 months (fingernails), 3 months (toenails)

* See **Potential ARV Interactions**, below, and **Common Medications**, p. 11.

Antifungal safety monitoring:

Terbinafine, itraconazole, and fluconazole can be hepatotoxic.

- Obtain pretreatment liver function values.
- Monitor for the development of hepatic symptoms.
- Monitor liver function in patients with underlying liver disease.

! POTENTIAL ARV INTERACTION

Pharmacokinetic interactions between many ARVs (PIs, NNRTIs, boosted integrase inhibitors, and maraviroc) and antifungal medications may significantly affect serum levels of the ARV or the antifungal medication. Some of these require dosage adjustment or careful monitoring, and some combinations are contraindicated. See **Common Medications**, p. 11 for further information.

Skin Cancer in Patients with HIV

There is an increase in both melanomas and non-melanoma skin cancers (basal cell carcinoma and squamous cell carcinoma) in patients with HIV.

In the Post-HAART era, patients with HIV have 1.5 times higher risks of melanoma and double the risk of non-melanoma skin cancers.

Although most non-melanoma skin cancers can be cured, they can be locally invasive and disfiguring if not treated early.

Risk factors for skin cancers include fair skin, positive family history, and cumulative sun-exposure.

The specific relationship of non-melanoma skin cancer to CD4 count and HIV viral load is uncertain, but ARV therapy use can be protective.

Due to the higher risks of skin cancers in patients with HIV, photoprotection, careful skin surveillance and early dermatologic referral are important.

Psoriasis

See photo at end of chapter.

Etiology	Findings/ Distribution	Diagnostic Clues	Management
<p>Activation of lymphocytes causes shortened epidermal life cycle (10 times shorter than normal), leading to epidermal hyperproliferation</p> <p>Tinea corporis and cutaneous T-cell lymphoma should be considered in the differential diagnosis.</p>	<p>Silvery scales on red plaques</p> <p>More common on extensor surfaces</p> <p>In HIV infection, can have unusual distribution, such as inverse psoriasis on palms and on soles of feet</p>	<p>More severe and more difficult to treat in patients with low CD4 cell counts</p> <p>Patients with CD4 counts of <200 cells/μL not on ARV therapy can have lesions on >50% of body.</p> <p>May see unusual presentations of inverse and diffuse psoriasis.</p> <p>Biopsy shows epidermal hyperplasia, parakeratosis, neutrophils, diminished granulosum layer.</p>	<p>For trunk / arms / legs: Clobetasol 0.05% ointment BID</p> <p>For face / axillae / groin / buttocks: Calcipotriene ointment BID</p> <p>Consider Derm referral for consideration of acitretin and/or narrowband UVB</p>

Topical Steroid Relative Potency (1 = least potent; 10 = most potent)

1	4	7	10
Hydrocortisone 1% cream/lotion/ointment	Triamcinolone (TAC) 0.1% cream/ointment Alclometasone 0.05% cream/ointment Desonide 0.05% cream/lotion/ointment	Fluocinonide (Lidex) 0.05% cream/gel/lotion/ointment	Clobetasol 0.05% cream/gel/ointment/solution

HPV-Associated Warts

See photo at end of chapter.

Etiology	Findings/ Diagnostic	Distribution Clues	Management
<p>Human papillomavirus; genital warts most commonly have subtypes 6, 11; also associated with dysplastic subtypes 16, 18, 31, 33, 35</p> <p>Worse and more difficult to treat in patients with low CD4 nadirs</p>	<p>Condyloma acuminatum: soft, skin-colored fleshy wart.</p> <p>Perianal lesions can be rough and cauliflower-like in and around genitalia and anus, around mouth, palmar surface of hands, on feet.</p>	<p>Can recur despite effective ARV therapy.</p>	<p>Can rarely recede on their own in 3 months.</p> <p>Start with liquid nitrogen (10-second bursts with 30-second thaw), podophyllin (for genital warts), or paring (for large lesions) every 3 weeks for 12 sessions; risk of dyspigmentation (particularly in darker skin) and scarring should be discussed.</p> <p>Patients can be instructed to use duct tape and other exfoliative techniques at home between office treatment sessions for lesions on the extremities only (not genital warts): apply duct tape nightly and pull off during the day; use pumice stone daily to sand down lesions).</p> <p>For genital warts, may add topical imiquimod 5% cream 3 times a week if initial treatment is not effective.</p> <p>Consider laser treatment, surgical excision (and send for pathologic exam to rule out dysplasia).</p> <p>Repeat treatments are usually required. Warts can recur after any of the treatment modalities.</p> <p>For anal lesions, see Anal Dysplasia, p. 315</p>

Rashes Associated with Antiretrovirals and Some Drugs Commonly Used in Patients with HIV

- Trimethoprim-sulfamethoxazole—very common-generalized erythematous morbiliform maculopapular eruption, fixed drug eruption, urticarial, SJS, TEN, erythema nodosum, erythema multiforme
- Dapsone: hypersensitivity syndrome (DHS) with fever, rash, eosinophilia, lymphadenopathy, hepatic and pulmonary manifestations
- Rifabutin: rash (11%), skin discoloration (<1%), pruritus.
- Rifampin: mild and self-limiting; and itching with or without a rash; Hypersensitivity (rare): pemphigoid reaction, SJS, TEN, DRESS
- Fluconazole: angioedema, pruritus, urticaria, erythematous or maculopapular rash, SJS, TEN, fixed drug eruption
- Itraconazole: urticaria
- Azithromycin: rarely angioedema, SJS, TEN
- Clarithromycin: rash in 3%

Table 1. Clinical Manifestations and Incidence of Antiretroviral Allergic Syndromes

Class	Agent	Reaction	Incidence	Discontinuation Rate
Protease Inhibitors	Atazanavir	Rash	≤6%	<1%
	Darunavir*	Rash SJS/TEN/DIHS/ DRESS	≤10% <1%	<1% 100%
	Fosamprenavir	Rash Moderate-Severe	≤1%	<1% <1%
	Lopinavir/Ritonavir	Rash	2%	<1%
	Tipranavir	Rash	≤10%	<1%
NNRTIs	Efavirenz**	Rash	4.6%-20%	<2%
		SJS/TEN DRESS/DIHS	0.1%	100%
	Etravirine	Rash	≤10%	<2%
		DRESS/DIHS, SJS/ TEN	<0.1%	100%

Class	Agent	Reaction	Incidence	Discontinuation Rate
-	Nevirapine	Rash	4-38%	6%
		DRESS/DIHS SJS/TEN	Up to 5% 0.3-1%	100%
	Rilpivirine	Rash	2%	<1%
	Nevirapine**	Rash, SJS, TEN	17-32%	2-10%
Fusion Inhibitors	Enfuvirtide	Hypersensitivity reaction	<1%	Mostly for subcutaneous reactions
NRTIs	Tenofovir	Rash	5%-7%	<1%
	Abacavir	Hypersensitivity reaction (see below) Rash only	5%-8% 3%	100% <1%
	Emtricitabine	Pruritus, rash	-	<1%
Integrase Inhibitors	Raltegravir	Pruritus, diaphoresis, rash	2-7%	<1%
		DRESS/DIHS/SJS/TEN	<1%	100%
	Maraviroc	Pruritus	3.8%	<1%

*There is no relationship between a history of rash to trimethoprim-sulfamethoxazole and allergy to darunavir.

**There may be cross-hypersensitivity between efavirenz and nevirapine.

DRESS = Drug Reaction with Eosinophilia and Systemic Symptoms

DIHS = Drug-Induced Hypersensitivity Syndrome

SJS = Stevens Johnson Syndrome

TEN = Toxic Epidermal Necrolysis

Abacavir hypersensitivity requires at least two symptoms of fever, rash, nausea, vomiting, headache, lethargy, myalgia, arthralgia or gastrointestinal symptoms, occurring within six weeks after commencement and resolving within 72 h of withdrawal of the drug. Less common manifestations include respiratory symptoms, paraesthesia, edema, renal or hepatic failure and anaphylaxis. HLA-B*5701 should be tested prior to abacavir initiation; it is a marker for ABC hypersensitivity and has 100% sensitivity in both U.S. Caucasian and African American.

Glossary of Dermatologic Descriptors

Cutaneous disorders commonly associated with HIV type-1 infection are classified as primary and secondary.

Primary Lesions

Bulla: a circumscribed fluid-filled lesion >1 cm in diameter that usually is elevated above the surrounding skin. May attain diameters of several cm and are described as tense or flaccid.

Macule: circumscribed area of skin, up to 1 cm in diameter, with a change from normal skin color, which is neither raised above nor depressed below the surrounding skin. Many use the term for lesions much larger than 1 cm. Term does not include purpura.

Nodule: discrete, solid, palpable, round or oval (ellipsoidal) lesion of the skin measuring ≤ 1 cm in diameter (or long axis). Applies to processes involving any or all levels of the skin, and is a general term for any mass, benign or malignant.

Papule: discrete solid area of skin that is elevated by palpation above the surrounding skin and <1 cm in diameter. Variations include acuminate, keratotic, flat-topped, follicular, umbilicated, pedunculated, and necrotic.

Patch: a flat, circumscribed, discoloration of skin or mucous membrane >1 cm in diameter.

Plaque: similar to a papule but >1 cm in diameter. Often formed by the confluence or coalescence of papules. Secondary features may include, among others, atrophy, lichenification, and hyperkeratosis.

Pustule: discrete elevated vesicle or bulla of skin, usually small, containing purulent exudate composed of inflammatory leukocytes (pus), with or without cellular debris. May be superficial, deep-seated, follicular, grouped, etc., and may arise secondarily from a vesicle.

Tumor: a term used by some for a nodule >1 cm in diameter. Applies to processes involving any or all levels of the skin, and is a general term for any mass, benign or malignant.

Vesicle: a circumscribed fluid-filled lesion <1 cm in diameter that usually is elevated above the surrounding skin. May be described as solitary, grouped, umbilicated, dyshidrotic, spongiotic, multilocular, or unilocular.

Wheal: an evanescent, round or irregular, often flat-topped elevation of skin with a pale red color, arising from edema in the superficial dermis. May vary from 2-3 mm to 10 or more cm in diameter, with round or arcuate configurations. Should be distinguished from angioedema, a massive edema involving the entire dermis and subcutaneous tissues.

Secondary Lesions

Atrophy: usually refers to thinning of the epidermis leaving an easily wrinkled or shiny surface. Atrophy also may apply to thinning of dermal or subcutaneous tissue, with or without changes in the epidermis.

Crust: dried surface fluid, often serous (inspissated serum), with or without tissue debris; includes the term scab.

Erosion: a superficial denudation of the skin, usually implying the loss of the epidermis.

Excoriation: a scratch mark, often with denudation of the skin to form a small ulcer. Exposure of the corium by mechanical removal of the epidermis.

Fissure: a vertical splitting or separation of the skin.

Lichenification: a thickening of the skin surface and an increase of skin markings, usually seen with chronic coalescence of papular lesions, especially atopic eczema.

Linear/Figurate: technically not secondary features, but included here for convenience. These are configurations that skin lesions may assume, and the descriptors aid in their diagnostic identification. Figurate includes geometrical shapes (e.g., annular, arciform, cyclic).

Scale: a thin flake of epithelium (mostly composed of corneocytes) that is separated from the underlying intact skin proper.

Scar: a hard plaque of dense fibrotic tissue covered by a thin epidermis. A mark of injury from any sort of process (physical or pathologic).

Ulcer: loss of skin tissue or substance from the surface downward, leaving an uncovered or denuded wound that is slow to heal.

Vegetating: a lushly growing, proliferating process, usually with elevated or exophytic features.

Grading of Rash Severity

Grade 1 (mild): localized skin eruption and/or limited skin eruption with or without pruritus

Grade 2 (moderate): diffuse eruption involving up to 50% of body surface area with or without superficial skin peeling, pruritus, or mucous membrane involvement and no ulceration

Grade 3 (severe): generalized rash involving **either** $\geq 50\%$ of body surface area **or** rash presenting with any of the following characteristics:

- Vesicles or bullae
- Superficial ulceration of mucous membranes
- Typical or atypical target lesions

- Palpable purpura/non-blanching erythema

Grade 4 (Life-threatening reactions)

- DRESS/DIHS



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Diabetes Mellitus

KEY POINTS

- Actively involve patients by providing information about HIV/AIDS and diabetes. Share decisions in a patient-centered way to jointly select a safe glycemic target and create an individualized treatment plan for HIV/AIDS and diabetes. Assess patient characteristics and non-glycemic factors when interpreting Hemoglobin A1c [HbA1c] results.
- Set HbA1c target ranges based upon absolute risk reduction of significant microvascular complications, life expectancy, and patient preferences.
- Develop individualized treatment plans based on complications, comorbidities, life expectancy and patient preferences.
- Recommend a Mediterranean diet if aligned to patient's values and preferences, otherwise a nutrition intervention strategy reducing percent of energy from carbohydrate to 14-45% per day and/or foods with lower glycemic index.
- Pharmaceutical agents should be selected based on efficacy, contraindications, drug interactions, comorbidities, potential side effects, and patient preferences.
- Risk stratification for and management of hypoglycemic events
- DSME may be delivered via various modalities, including group sessions/discussion, telephone, web-based technology, multimedia presentations, teach-back, and role play.



BACKGROUND

Diabetes is the leading cause of major health complications such as end stage renal disease and lower extremity amputations and is a significant contributor to ischemic heart disease, stroke, peripheral vascular disease and vision loss. There is increasing acceptance over many years of the importance of individualizing glycemic management and in the risk of adverse events, especially hypoglycemia. This is of great importance for all patients, especially those 65 years and older with comorbid conditions. In 2013 there were 12.0 million older adults (≥ 65 years) in the U.S. with diabetes, comprising 40% of the 30.2 million patients with diabetes. Older adults comprise an estimated 60-70% (unpublished data) of the Veterans Affairs (VA) and Department of Defense (DoD) diabetes population (largely retirees). These considerations make safe and effective diabetes management an important priority for all clinicians.

The 2017 VA/DoD Clinical Practice Guideline (CPG) for the Management of Diabetes Mellitus offers healthcare providers an evidence-based framework to evaluate, treat, and manage persons with type 2 diabetes mellitus in the context of their individual needs and preferences with respect to glycemic management.

Note: Some medications mentioned in this chapter may not be available on the VHA National Formulary (<https://www.pbm.va.gov/NationalFormulary.asp>). Consult VA pharmacists for alternatives

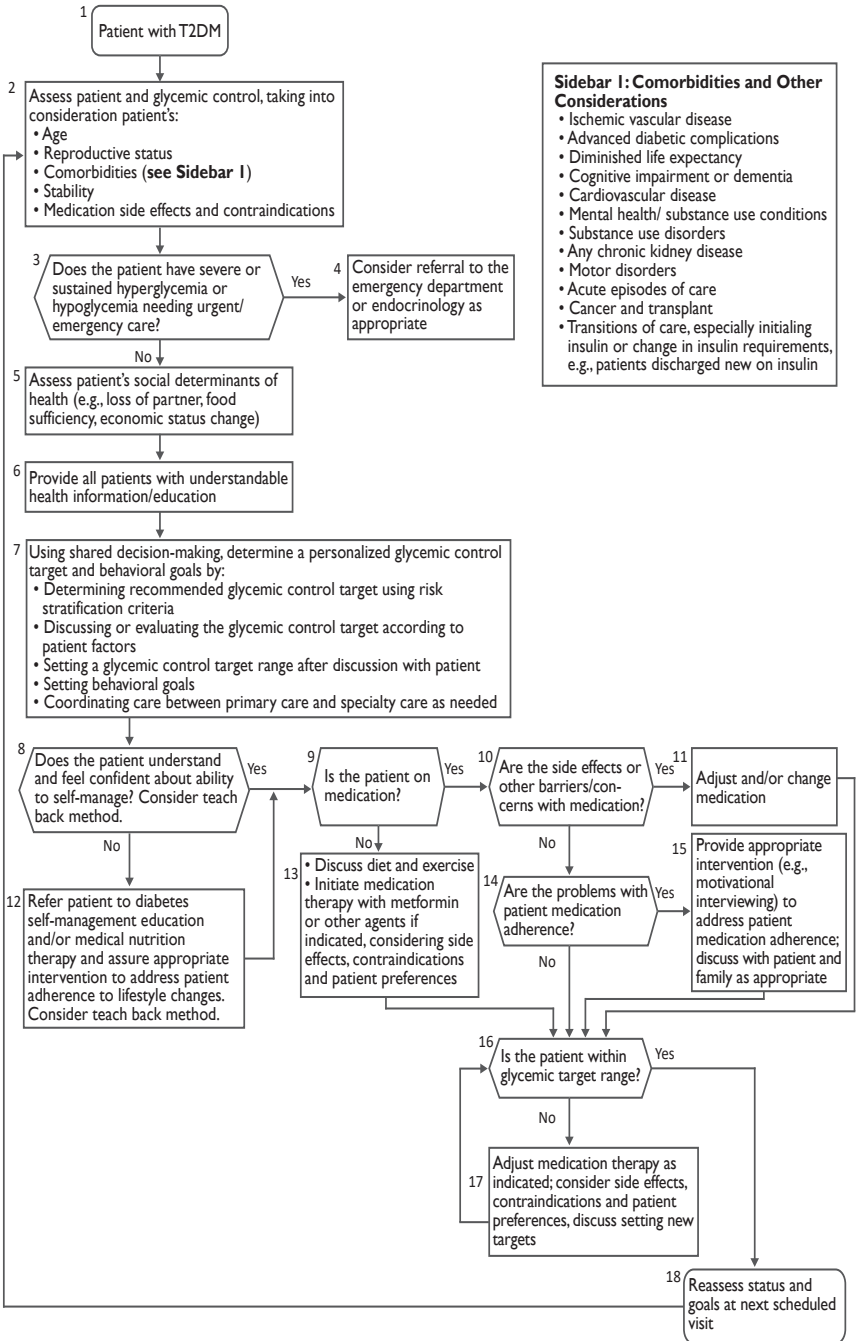
It provides practice recommendations for the care of patients with diabetes with special emphasis on shared decision making.

The full guidelines, summaries for clinicians and patients, and tools are available on the Quality, Safety, Value, <https://www.healthquality.va.gov/guidelines/CD/diabetes/>. A synopsis published in the Annals of Internal Medicine is available at <https://annals.org/aim/fullarticle/2659342/synopsis-2017-u-s-department-veterans-affairs-u-s-department#multimedia>.

All clinicians and teams providing care to patients with type 2 Diabetes should refer first to the algorithm, which is a sequential approach to the patient with diabetes. Identification of risks, including hypoglycemia and hyperglycemia occurs first; nutrition therapy impacts all patients at each stage of diabetes (and pre-diabetes), and assess food insecurity. Conveying complex information in an understandable manner to individual patients and families through a formal process of shared decision making is foundational to setting and revising goals that are meaningful, safe, and achievable in every day clinical practice.

Management of common co-existing conditions associated with diabetes, including obesity, dyslipidemia, hypertension, cardiovascular disease, depression, and substance use are covered in other VA/DoD Guidelines.

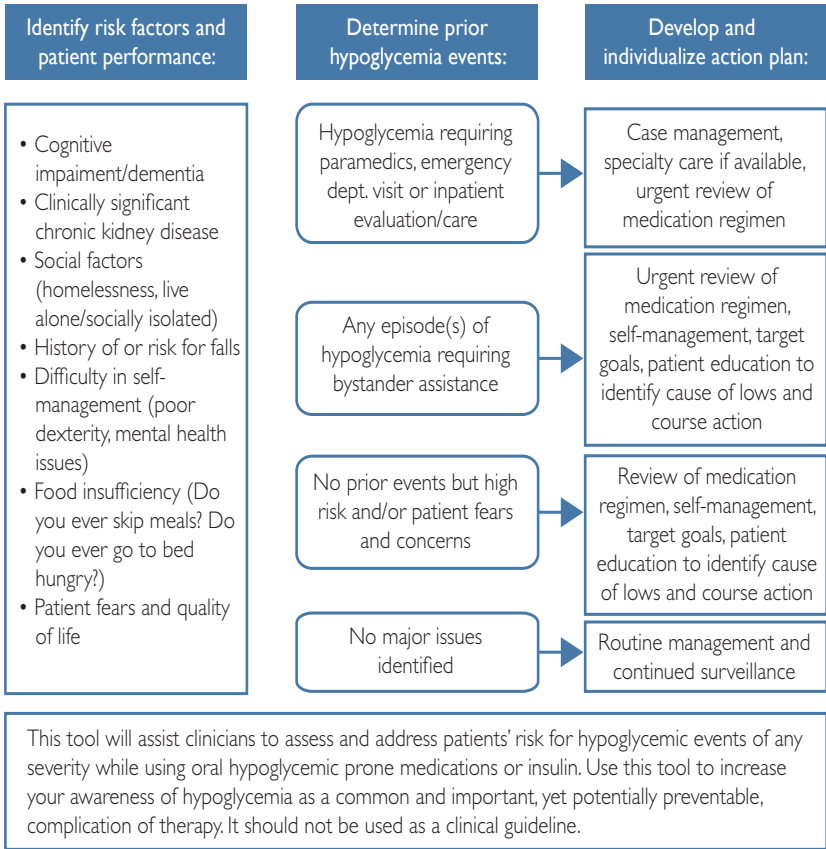
Algorithm for Glycemic Management



Sidebar I: Comorbidities and Other Considerations

- Ischemic vascular disease
- Advanced diabetic complications
- Diminished life expectancy
- Cognitive impairment or dementia
- Cardiovascular disease
- Mental health/ substance use conditions
- Substance use disorders
- Any chronic kidney disease
- Motor disorders
- Acute episodes of care
- Cancer and transplant
- Transitions of care, especially initiating insulin or change in insulin requirements, e.g., patients discharged new on insulin

Risk Stratification Tool for Hypoglycemia and Action Steps



Developed in collaboration with the Federal Interagency Work Group-Diabetes Agents/ Department of Health and Human Services (S/2017).

Nutrition and Food Insecurity

With the introduction and advancement of highly active antiretroviral therapy (HAART) there has been an alteration in the metabolic and nutritional profile of those with HIV/AIDS. In the past, nutrition assessment, diagnosis and intervention focused on the prevention of wasting and the prevention of foodborne illness. The metabolic and nutritional parameters of the HIV/AIDS population have shifted.

The nutrition care process evaluates the metabolic and nutritional factors including peripheral lipoatrophy; increased waist-hip ratio; increased prevalence of metabolic syndrome; prediabetes and diabetes which have emerged as metabolic issues in those receiving HAART for HIV/AIDSs.

Individualized baseline and ongoing nutrition assessment evaluating weight history, BMI, diet history, psychosocial access to food, food / drug interactions, CD4 count viral load, albumin, pre-albumin, Vit B12, folate, Mg, Fe studies, fasting lipids and glucose values are required in the determination of the individualized nutrition intervention strategy.

For patients living with HIV/AIDS, the goals of nutrition intervention and follow-up include assessment of energy needs along with micro and macronutrient needs to maintain nutritional status and quality of life. The 2017 VA/DoD Clinical Practice Guideline for the Management of Type 2 Diabetes Mellitus in Primary Care added two strong recommendations for nutrition intervention strategies in diabetes. The first recommendation is to follow a Mediterranean style diet, if this resonates with the patient's values and preferences. For patients with the diagnosis of HIV/AIDS, assessment of energy needs with the goal of weight maintenance is typical. An increased intake of omega 3 fatty acids with a reduced intake of saturated fat, trans fat and cholesterol is typically advised. Moderate carbohydrate intake to include 3-5 servings daily of fruits and vegetables along with 20-35 gms per day of dietary fiber of which at least 10 gms is soluble form is advised.

The 2017 VA/DoD guidelines Clinical Practice Guideline for the Management of Type 2 Diabetes Mellitus in Primary Care strong recommendation for a Mediterranean style diet as a nutrition intervention strategy aligns the above stated nutrition goals of this population. There is known variation in the cuisine of Mediterranean countries, but certain features are commonly used to describe a traditional Mediterranean diet such as: high intake of vegetables, fruits, nuts, unrefined grains, and olive oil; moderate intake of fish and poultry; and low intake of red meat, processed meat, dairy, and sweets. The Mediterranean-style dietary pattern is effective in improving glycemic control, delaying the time to first pharmacological intervention, and reduces cardiovascular risk factors in patients with diabetes. Additional benefits of this dietary pattern include significant hemoglobin A1c (HbA1c) reduction. A Mediterranean diet has also been linked to improved cardiovascular outcomes and weight loss. In general, the evidence to support eating a Mediterranean diet is robust but securing and adapting to these types of foods may be challenging.

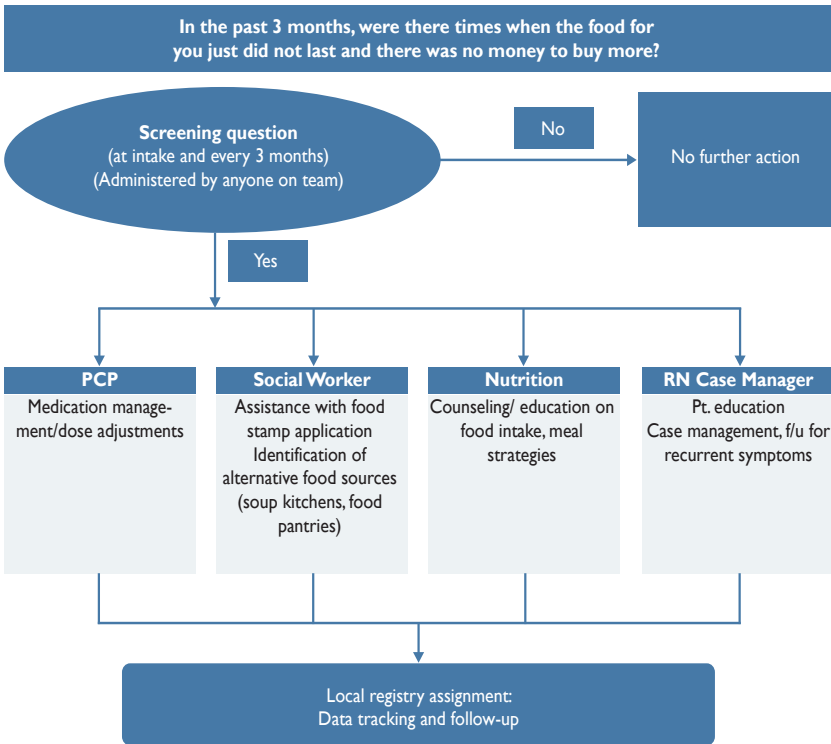
The second nutrition recommendation is to reduce the percent of energy from carbohydrates to 14-45% per day and/or eat foods with lower glycemic index. This dietary pattern may be employed in patients who do not choose the Mediterranean diet. A systematic review compared dietary interventions including lower carbohydrate and low glycemic index nutrition intervention strategies which may lead to improve glycemic control, lipid profiles and body mass index.

Food safety remains of key importance in the HIV/AIDS population. Patients who do not have HIV are typically able to fight off bacteria from contaminated foods. Even with the introduction and advancement of HAART, Campylobacter and salmonella frequency rates remain much higher in the HIV population than the general population. Food safety advice including the importance of washing hands

with soapy water for at least 20 seconds before and after handling or preparing food is very important. Additional food safety education in this population should include:

- avoidance of raw seafood, including sushi, clams on the half shell
- avoidance of unpasteurized dairy products
- avoidance of soft boiled eggs or sunny side up eggs
- leftovers should not be stored for more than 2 days in the refrigerator
- leftovers should be reheated to $> 140^{\circ}\text{F}$
- paper towels are to replace dishtowels in the kitchen.

Food Insecurity Screening Algorithm



Food insecurity is another important consideration in diabetes. The consequences of food insecurity are significant and potentially life-threatening. One study documented the inherent risks from low blood sugar among elderly patients with diabetes who have other significant illnesses and don't have a stable source of food. Hypoglycemia, cognitive dysfunction, and an increased risk of falls are just some of the complications and consequences of food insecurity. Another study found that risk for hospital admissions for hypoglycemia increased 27% in

the last week of the month among low-income populations, typically when food stamps and supplies at food pantries ran low or were exhausted.

Among those reporting food insecurity in a recent study of Veterans Clinics for the Homeless, relying on food from soup kitchens and food pantries (22.9%), shelters (14.5%), and help from friends or family (19.1%); 47.3% were receiving food stamps, and 26% were in a transitional housing program where they were responsible for some of their meals. 27.3% reported only one meal per day. Overall, 22.1% had depression, 22.0% had psychoses, 25.2% abused alcohol, and 19.8% had diabetes or prediabetes; 43.5% reported that they experienced hypoglycemia symptoms (e.g., anxiety, sweating, chest pain) when without food. The figure above describes the screening process, how health care providers addressed patients who were food insecure, and data collection and follow-up.

Patient Centered Care and Shared Decision Making (SDM)

Shared decision making (SDM) permits patients and their providers and health care team to jointly create an individualized care plan that is tailored to each patient's clinical condition, goals, lifestyle and preferences. SDM reinforces a trusted therapeutic relationship, increases patient satisfaction and treatment "buy-in" regarding the ways and methods to reach that particular goal or treatment plan. Key principles include the patient/family readiness, tools with understandable information about the benefits and harms of all options, and strategies to identify and incorporate their preferences. Patients cannot effectively participate in care and share decisions unless they understand diabetes and HIV and how they can be involved in planning and carrying out the jointly developed diabetes and HIV care plan. Patient information should be culturally appropriate and also understandable and actionable by patients with limited literacy skills. It should be accessible to patients with physical, sensory or learning needs.

SDM should not be used just for patients with stable glycemic control and HIV treatment plans. It should also be used to assist patients who may not be able or willing to make lifestyle changes and decisions that affect their diabetes and HIV disease at any time during the course of treatment. SDM should be included, at a minimum, at the time of diagnosis, during difficulties with management, at times of transition or changes to the plan of care or development of complications.

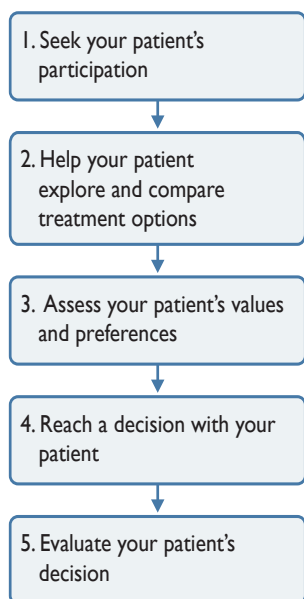
Benefits include greater knowledge of medications and understanding of risks. In addition, patient centered care and SDM together may decrease patient anxiety, increase trust in clinicians and improve treatment adherence. Family involvement should be considered if appropriate, especially in older adults.

As part of the patient centered care approach to diabetes management and HIV, clinicians should explore with the patient the outcomes of previous opportunities for SDM, their ability to self-manage, prior efforts to change health behaviors, past treatment experiences (including reasons for discontinuing treatment), and relevant clinical outcomes. In actively sharing decisions, clinicians should

involve the patient in prioritizing problems to be addressed and in setting specific goals regardless of the selected setting or level of care.

The Agency for Healthcare Research and Quality's (AHRQ) SHARE Approach provides a framework on sharing decisions with patients. Patients' understanding of their clinical conditions and possible treatment options is the foundation of SDM. For this reason, it is important for clinicians to determine whether the information and explanations they have provided to the patient have been clear. The Teach Back technique is an easy way to do this in time-limited clinical encounters.

AHRQ SHARE Approach



To share decisions about treatment options, patients need information that they can understand about their condition and treatment choices. To quickly find out how well the patient understood what you discussed, use Teach Back. You can find out in 1-2 minutes using questions like this:

- “We talked about two ways that you might be able to treat your diabetes: either starting medicine right away to lower your blood sugar or increasing your physical activity and following a Mediterranean diet to try to lose a little weight. I want to make sure I explained each option clearly. Would you please tell me how you would explain the two choices to a member of your family?”
 - “I want to make sure I was clear about the risks and benefits of taking insulin to control your diabetes. Could you tell me about insulin's possible side effects and how it might impact your life on a day-to-day basis?”
- **If the patient did not understand, say “I must not have done a good job explaining. Let me try again.” And use a different approach.**

A1c Target Ranges

Set HbA1c target ranges based on absolute risk reduction of significant microvascular complications, life expectancy, and patient preferences.

Glycemic Targets – VA/DoD 2017

“We recommend setting an HbA1c target **RANGE** based on absolute risk reduction of significant microvascular complications, life expectancy, patient preferences and social determinants of health.”

Major Comorbidities or Physiologic Age	Microvascular Complications		
	Absent or Mild	Moderate	Advanced
Absent >10-15 years life expectancy	6.0-7.0%	7.0-8.0%	7.5-8.5%
Present 5-10 years life expectancy	7.0-8.0%	7.5-8.5%	7.5-8.5%
Marked <5 years life expectancy	8.0-9.0%	8.0-9.0%	8.0-9.0%

The CPG proposes HbA1c target ranges, rather than an all-or-none target value, based on the presence or absence of microvascular complications, comorbidities, and life expectancy. This is rooted in the substantial body of evidence showing a direct relationship between glucose control and microvascular complications (e.g., retinopathy, neuropathy and nephropathy). The overarching goal of these recommendations is to develop individualized treatment plans and HbA1c target ranges that are tailored to a patient’s unique characteristics and goals of care.

Higher levels of HbA1c carry greater risk of complications and lowering HbA1c prospectively reduces risk. The relationship between HbA1c and the risk of microvascular complications is continuous, and accelerates with HbA1c levels >9%. While there is no apparent HbA1c threshold above which benefits are not accrued by lowering HbA1c, however, the absolute risk reduction is markedly less at lower levels of HbA1c. Thus, a decrease in HbA1c may have minimal clinical impact on complications in patients with limited life expectancies. Conversely, there are no data on the appropriate lower limit for achieved HbA1c, albeit there are strong data on the risks of hypoglycemia as HbA1c is targeted to near normal levels for patients receiving insulin. Lower levels of HbA1c (closer to 6%) may be reasonable in younger patients treated with metformin alone.

Microvascular complications develop over an extended period of time. Thus, patients with longer life expectancy and absent or mild microvascular complications (e.g., early background retinopathy, microalbuminuria, or mild neuropathy) may benefit from lower HbA1c (i.e., 6.0-7.0%).

Definitions of Microvascular Comorbidities

Mild: early retinopathy, and/or microalbuminuria, and/or mild neuropathy

Moderate: pre-proliferative retinopathy or persistent, fixed proteinuria (microalbuminuria), and/or demonstrable peripheral neuropathy (sensory loss)

Advanced: serve non-proliferative or proliferative retinopathy and/or renal insufficiency (Stage 3b CKD), and/or insensate extremities or autonomic neuropathy (e.g., gastroparesis, impaired sweating, orthostatic hypotension)

For patients with comorbidities and/or complications that shorten life expectancy (<10 years), higher HbA1c target ranges are appropriate. Systematic reviews comparing intensive and conventional glucose control showed no statistically significant differences in all-cause mortality or death from cardiovascular disease, but did show statistically significant risk reduction for microvascular complications such as nephropathy, retinopathy, and lower extremity amputation (36-38). Indeed, these trials provided no firm evidence that lowering HbA1c to <8.5% reduces risk of death from cardiovascular disease. Depending upon the presence of and degree of microvascular complications, HbA1c target ranges of 7.0-8.0% or 7.5-8.5% are appropriate for most patients.

The presence of major comorbidities that shorten life expectancy (<5 years) or advanced microvascular complications (e.g. severe non-proliferative or proliferative retinopathy, renal insufficiency [Stage 3b or greater chronic kidney disease], insensate extremities or autonomic neuropathy) may justify a higher HbA1c target range. Such patients are less likely to benefit from intensive glucose control and more likely to experience risks from treatment.

Intensive glucose control (defined as HbA1c <7%) may cause frank harms such as increased risk of death from cardiovascular events and severe hypoglycemia (i.e., requiring help from another person). However, most episodes of serious hypoglycemia occur at higher HbA1c values. Risk factors associated with hypoglycemia include use of specific drugs (insulin and sulfonylureas), older age (>75 years), cognitive impairment, and chronic kidney disease (including causes unrelated to diabetic nephropathy), and social determinants of health.

Set HbA1c Target Ranges Based Upon Absolute Risk Reduction of Significant Microvascular Complications, Life Expectancy, and Patient Preferences

The VA/DoD Diabetes Clinical Practice guidelines note that for summarizing evidence, estimates of absolute risk, rather than relative risk should be consistently provided for both benefits and harms or burdens. Within the context of Shared Decision Making (SDM) it is important for both clinicians and patients to understand the risks associated with treatment options.

According to a 2011 Cochrane review, there are strong logical arguments for not reporting relative values alone, as they do not allow a fair comparison of benefits and harms as absolute values do. Their review indicated that both health professionals and consumers alike may change their choices when the same risks and risk reductions are presented using alternative statistical formats. On average, they found perceived risk reductions to be larger and are more likelihood of being persuaded to adopt a health intervention when its effect is presented

in relative terms (e.g. using relative risk reduction which represents a proportional reduction) rather than in absolute terms (e.g. using absolute risk reduction which represents a simple difference).

Relative risk reduction

Relative risk measures how much the risk is reduced in the experimental group compared to a control group. The formula for computing relative risk reduction is: $(\text{CER} - \text{EER})/\text{CER}$. CER is the control group event rate and EER is the experimental group event rate.

Absolute risk reduction

Absolute risk reduction (ARR) is just the absolute difference in outcome rates between the control and treatment groups: $\text{CER} - \text{EER}$.

Number needed to treat

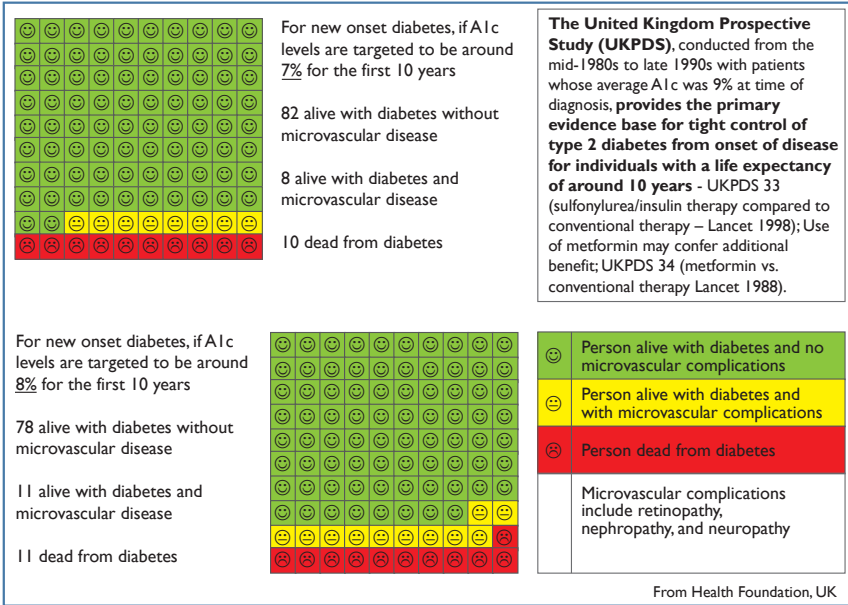
The number needed to treat is another way to express the absolute risk reduction. It is $1/\text{ARR}$ and can be thought of as the number of patients that would need to be treated to prevent one additional bad outcome.

NNT is often presented with the assistance of Cates Plots. Dr. Chris Cates developed the use of smiley face plots to visually communicate the risks and benefits of treatment as patients aids. See **Figure 1**.

As another clinical example on how framing of trial results differs, we can use the results from the United Kingdom Prospective Diabetes Study 33 (UKPDS) which showed that the major benefit of lowering HbA1c from 7.9% (average) to 7.0% (average) over 10 years for recent onset disease was prevention of advanced microvascular complication, predominantly laser photocoagulation (absolute risk reduction was 3.1/100 patients treated for 10 years). The ARR of any microvascular complication was 5.0/100 and the number needed to treat was 19.6. The relative risk reduction was a 37% decrease in risk for microvascular complications and was continuous and without a threshold. However, the ARR for each 1% reduction in HbA1c was less at lower levels of initial HbA1c. The microvascular benefit was sustained for 10 years after the trial was completed, although the average HbA1c values converged in the treatment groups.

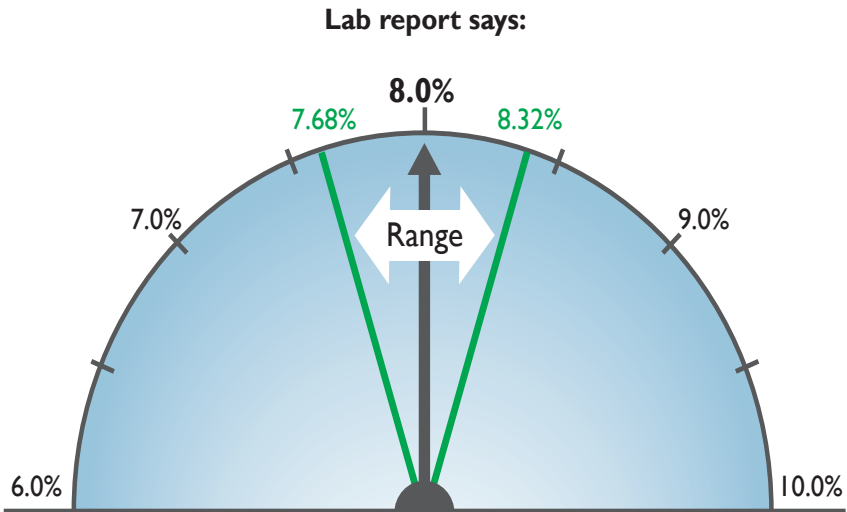
Cates Plot

The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med.* 1993;329:977– 986. <https://www.iwh.on.ca/wrmb/absolute-and-relative-risk>; <http://www.thennt.com/thennt-explained/>



In summary, it is important to understand that relative risks may appear to make the benefits bigger while absolute risk can minimize the actual benefits while number needed to treat has important clinical ramifications in health care policy. Understanding the difference between the numbers can avoid confusion and provide more decision making clarity of the inherent the risks and benefits of treatment. Relative risk reduction values alone, which often market better, do not allow a fair comparison of benefits and harms as absolute values do. Understanding the difference in diabetes can mean the risk of medication overuse with potential for serious consequences such as hypoglycemia, untoward drug side effects and even possible death.

Assess Patient Characteristics and Non-Glycemic Factors When Interpreting Hemoglobin A1c (HbA1c)



The A1c test provides information about a patient's average blood glucose levels over the past 3 months. An A1c test result is not an absolute number; it is a number within a range. The range depends both upon the specific laboratory A1c method used and the quality of the laboratory performing the test. The test precision is measured by coefficient of variation (CV). For example, a reported A1c result of 8.0% is actually in a range of ~7.7% to 8.3% from a high-quality laboratory in which the assay CV is 3%. A1c results should be interpreted in the context of home blood glucose testing, and medications should not be changed based upon a single result that falls within the assay range.

Many factors affect the measurement of HbA1c besides the level of glycemia. Since HbA1c is dependent on the duration of erythrocytes exposure to glucose, conditions that alter erythrocyte life span will affect the measured level of HbA1c. Iron deficiency anemia, which prolongs red cell life and exposes the cell to glucose for a longer period of time, is associated with false elevations of HbA1c. In contrast, conditions that reduce red cell life span (e.g., hemolytic anemia) may result in falsely low HbA1c levels. A variety of other conditions may result in alterations in HbA1c measurement (e.g., chronic kidney disease). Hemoglobin variants can result in falsely elevated or falsely lowered HbA1c, depending on the specific assay used. In addition, oral hypoglycemic agents (metformin or sulfonylureas) may alter the relationship between blood glucose levels and HbA1c, although the clinical significance is unclear.

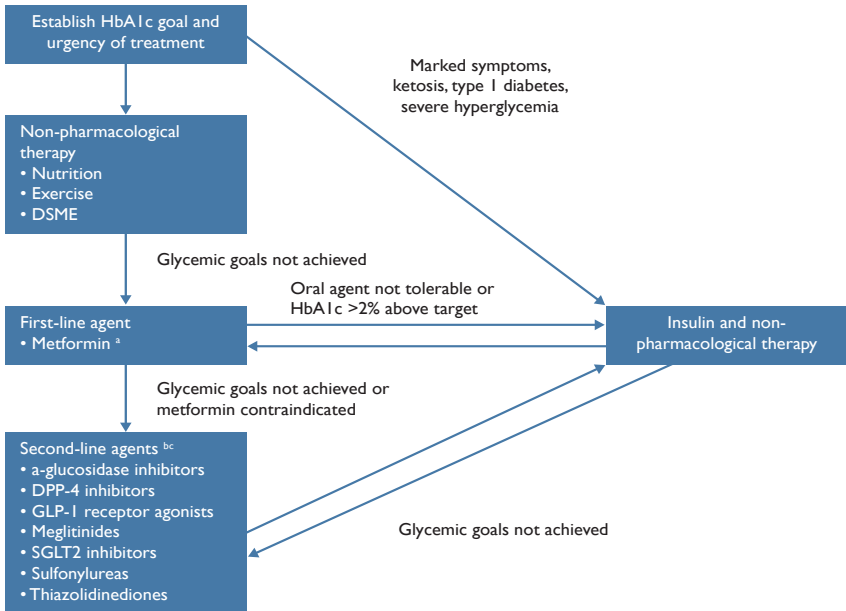
There are also racial/ethnic differences in HbA1c levels for a given level of glycemia. African Americans with prediabetes had HbA1c values 0.4% higher than whites; those who were within 3 years of diagnosis similarly had higher

HbA1c values than whites for any measure of glycemia. This difference cannot be explained by measured differences in glycemia, clinical factors known to affect HbA1c measurement, or sociodemographic factors.

Therefore, it is recommended that a new diagnosis of diabetes be based upon a confirmatory fasting blood glucose level ≥ 7.0 mmol/L (126 mg/dL) if the initial HbA1c value is 6.5 - 6.9%.

How and where the HbA1c level is measured can also affect results because of intra-laboratory variation (the variation in test accuracy and precision) and inter-laboratory variation (variation related to using different methodologies for the tests themselves). A single HbA1c measurement, even from a high-quality laboratory, has a margin of error so that the true value is within a range defined by the coefficient of variation. Sequential HbA1c values that are within 0.5% HbA1c are not statistically different from one another unless the assay coefficient of variation is $< 3\%$, and ideally $< 2\%$ (29). Treatment decisions based upon a single HbA1c level alone without consideration for other clinical data such as glucose monitoring results may lead to unnecessary initiation or intensification of therapy. Comparing HbA1c tests performed in different clinical laboratories introduces another source of error, as does use of point-of-care HbA1c testing, which is not subject to systematic quality oversight. Assessing the impact of these patient characteristics and non-glycemic factors that affect HbA1c levels allows for better individualization of management. For all of these reasons, the VA/DoD does not recommend the use of estimated average glucose (eAG).

Pharmacological Therapy



For more information on medications, see the Clinical Practice Guidelines website, <https://www.healthquality.va.gov/guidelines/cd/diabetes/>.

Abbreviations: DPP-4: dipeptidyl peptidase-4; DSME: diabetes self-management and education; GLP-1: glucagon-like peptide-1; SGLT2: sodium glucose co-transporter 2

* Bile acid sequestrants, bromocriptine quick release, and pramlintide are uncommonly used agents in the management of diabetes and are not included in this guideline.

^a Consider a trial of metformin extended-release in those with persistent adverse gastrointestinal effects from metformin immediate-release.

^b Second-line agents listed alphabetically; not in order of preference

^c If applicable, refer to VA, <http://www.pbm.va.gov/> or DoD, <http://www.health.mil/PandTguidance/> criteria for further recommendations on use of these agents.

The evidence for pharmacological treatment options for T2DM was not systematically reviewed as part of this guideline update; therefore, formal recommendations could not be made. The rationale to not systematically review the evidence for pharmacotherapy was that the evidence in this area is rapidly evolving and therefore any recommendations made may be outdated during the lifetime of this guideline. In lieu of recommendations, the following considerations are offered based on usual care and recent SRs performed by other groups. Where applicable, users of this guideline are asked to refer to their respective agencies for guidance/criteria on the use of pharmacotherapy for T2DM that are based on the most current evidence. The interactions between anti-viral therapy and anti-glycemic agents is reviewed in **Substance Use**, p. 107.

The following considerations are based on usual care and SRs performed by other groups:

1. When selecting an agent, consideration must be given to efficacy, contraindications, drug interactions, comorbidities, and potential side effects. Discuss with patients the various treatment options and arrive at a shared treatment plan.
2. Insulin should be considered as initial therapy in any patient with hyperglycemia with significant symptoms, if ketosis is present, and in newly diagnosed or previously unrecognized T1DM.
3. Metformin should be given as the first-line agent unless there are contraindications.
4. In patients with metformin intolerance or contraindications, other drug classes can be considered. These include (not in order of preference): alpha-glucosidase inhibitors (AGIs), dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) agonists, insulin, meglitinides, sodium glucose co-transporter 2 (SGLT2) inhibitors, sulfonylureas (SU), and thiazolidinediones (TZDs).

5. When initial therapy no longer provides adequate glycemic control, addition of a second-line agent from another class rather than substitution is usually necessary. Substitution can be reserved for intolerance/adverse effect to a drug. Combination of two anti-hyperglycemic drugs has the benefit of reducing hyperglycemia by working on different mechanisms that cause hyperglycemia (refer to **Figure I**). Some agents are not generally used in combination or have not been studied in combination (refer to **Appendix C**). Although the evidence is clear on the relative efficacy of the various medications, their usage needs to be guided by clinical considerations.
6. Addition of basal insulin to existing regimen should be considered, particularly if the desired decrease in HbA1c is not likely to be achieved by use of combination therapy.
7. Patients and their families should be instructed to recognize and confirm their understanding of signs and symptoms of hypoglycemia and its management.
8. Given that new studies and FDA alerts will be published subsequent to the release of this guideline, clinicians should refer to the criteria for use published by the VA Pharmacy Benefits Management program (VA PBM) and the Department of Defense Pharmacy and Therapeutics Committee (DoD P&T).

VA Materials

Health Information on HIV/AIDS and Diabetes for Patients and the Public

The Veterans Health Library (VHL) provides Veteran-focused, VA vetted health information on HIV/AIDS and diabetes including health sheets and videos, <http://www.veteranshealthlibrary.org>.

You can find more information on preventing Low Blood Sugar on https://www.prevention.va.gov/Talk_with_Your_VA_Provider_to_Avoid_Low_Blood_Sugar.asp.

VA/DoD Guidelines

Management of Diabetes Mellitus in Primary Care (2017)

The guideline describes the critical decision points in the Management of Diabetes Mellitus (DM) and provides clear and comprehensive evidence based recommendations incorporating current information and practices for practitioners throughout the DoD and VA Health Care systems. The guideline is intended to improve patient outcomes and local management of patients with diabetes mellitus. Tools and links to related guidelines (Hypertension, Dyslipidemia, and

Chronic Kidney Disease) are available at <https://www.healthquality.va.gov/guidelines/CD/diabetes/>.

1. VA/DoD Clinical Practice Guidelines. Management of Diabetes Mellitus in Primary Care (2017), <https://www.healthquality.va.gov/guidelines/CD/diabetes/>.
2. U.S. Department of Veteran Affairs, U.S. Department of Defense. Veterans Health Administration, Office of Quality and Performance, Evidence Review Subgroup. VA/DoD clinical practice guidelines: CPG policy guidance: guideline for guidelines. Revised 10 April 2013, <https://www.healthquality.va.gov/policy/index.asp>.
3. Annals of Internal Medicine article on the Synopsis of the VA/DOD Diabetes Guidelines and accompanying video on A1c test interpretation, <http://annals.org/aim/fullarticle/2659342/synopsis-2017-u-s-department-veterans-affairs-u-s-department#multimedia>.

VA Choosing Wisely-Hypoglycemic Safety Initiative

This initiative focuses on prevention of hypoglycemia, a major adverse drug event for older patients in the United States, https://www.qualityandsafety.va.gov/ChoosingWiselyHealthSafetyInitiative/HypoglycemiaSite/For_Clinicians.asp

Federal Tools

Clinicians

The Health and Human Services Hypoglycemia Risk Stratification Tool Developed by the Federal Interagency Coordinating Committee: Included in VA/DoD Tool Kit, <https://www.hiv.va.gov/pdf/pcm-diabetes-f01.pdf>.

Diabetes & Prediabetes Tests

NIDDK Diabetes Clearinghouse, <https://www.niddk.nih.gov/health-information/diagnostic-tests/diabetes-prediabetes>.

Shared Decision Making and Teachback

The SHARE Approach. AHRQ, <https://www.ahrq.gov/professionals/education/curriculum-tools/shareddecisionmaking/index.html>.

Preventing Adverse Drug Events: Individualizing Glycemic Targets Using Health Literacy Strategies is an eLearning course that teaches health care providers how to reduce hypoglycemic adverse drug events (ADEs) in patients with diabetes. (Office of Disease Prevention and Health Promotion). Includes videos:

<https://health.gov/hcq/trainings/ade-diabetes-agents/>

<https://health.gov/hcq/training-prevent-ade.asp>

Pharmacy Benefits Management Services. Veterans Health Administration, <https://www.pbm.va.gov/>.

Patients

The A1C Test & Diabetes: NIDDK Diabetes Clearinghouse, <https://www.niddk.nih.gov/health-information/diabetes/overview/tests-diagnosis/a1c-test>.



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Dyslipidemia

KEY POINTS

- HIV infection itself and certain ARV medications may cause lipid abnormalities.
- Patients should be treated for dyslipidemia based on their lipid levels and other risk factors for cardiovascular (CV) disease.
- Some lipid-lowering medications are contraindicated for use with ARV medications, and others require dosage adjustment.



BACKGROUND

- Dyslipidemia is an important risk factor for CV disease, and occurs in a high proportion of HIV patients. As advances in ARV therapy extend the lifespans of people with HIV infection, it is likely that morbidity and mortality from CV disease will increase. It is important to identify patients' CV risk factors and to reduce those that are modifiable.
- CV risk is associated with the following lipid abnormalities:
 - Elevated LDL and total cholesterol (TC)
 - Low HDL
 - Elevated TGOf these, elevated LDL is most closely linked to CV risk, and usually is the primary target of therapeutic interventions.
- Dyslipidemia is associated both with HIV infection itself and with ARV medications. Accumulating data suggest that both HIV infection and certain ARV medications may increase the risk of CV disease, independent of their effects on lipids.
- Patients with untreated HIV infection commonly show:
 - ↓ TC
 - ↓ LDL cholesterol
 - ↓ HDL cholesterol
 - ↑ TG
- Patients treated with ARV medications commonly show:
 - ↑ TC, LDL, and TG levels
 - Low HDL
- Dyslipidemia among patients taking ARV medications is probably related to multiple factors, including:

Note: Some medications mentioned in this chapter may not be available on the VHA National Formulary (<https://www.pbm.va.gov/NationalFormulary.asp>). Consult VA pharmacists for alternatives.

- Individual patient characteristics (comorbid conditions, diet, genetic background, exercise)
- HIV infection itself
- ARV medications
- Certain agents in each of the 3 major classes of ARVs may cause lipid abnormalities.
 - PIs: may markedly ↑ TC, LDL, and TG levels (particularly ritonavir and higher dose RTV boosted PIs; unboosted atazanavir does not typically affect lipids; atazanavir and darunavir boosted with only 100 mg per day of ritonavir or 150 mg of cobicistat have minimal effects on lipids in most patients.
 - NNRTIs: variable increases occur with efavirenz; nevirapine, rilpivirine and etravirine are less likely to cause abnormalities.
 - NRTIs: stavudine may ↑ TC and TG; Tenofovir disoproxil fumarate (TDF) reduces TC; tenofovir alafenamide (TAF) has a neutral effect.
 - Fusion inhibitors, CCR5 antagonists, integrase inhibitors: not associated with dyslipidemia
- For patients with CHD or CHD risk equivalents (see below), if possible, select ARV regimen to minimize the risk of dyslipidemia.



SCREENING

- Check fasting lipids before starting ARV therapy.
- Check fasting lipids 1-3 months after starting or changing ARVs.
 - If normal: screen at least once per year.
 - If abnormal: monitor closely until LDL goal is achieved.



EVALUATION

Note: The following recommendations are based on **National Cholesterol Education Program (NCEP) guidelines** for the evaluation and management of dyslipidemia. These are widely used, but have not been validated in patients with HIV infection. In 2003, the HIV Medical Association (HIVMA) of the Infectious Disease Society of American (IDSA) and AIDS Clinical Trials Group (ACTG) recommended using these guidelines as did the HIVMA IDSA Primary Care Guidelines in 2013. An alternate approach to assessing patient risk for CVD and determining when to start and monitor therapy has been proposed by the American College of Cardiology and the American Heart Association (ACC/AHA). The relative applicability of the NCEP and ACC/AHA guidelines in HIV-infected patients has not been fully determined.

History

The need for lipid management is based on lipid levels and on risk factors for coronary artery disease events. In the history, the American College of Emergency Physicians (ACEP) guidelines focus on factors that suggest CHD, CHD equivalents, or CV risk.

- **CHD risk equivalent:** considered equal in risk to known CHD
- **CHD risk factor:** a condition associated with greater risk of serious cardiac events

CHD	CHD Risk Equivalents	CHD Risk Factors
<ul style="list-style-type: none"> • History of MI • Unstable angina • Stable angina • CHD procedures • Evidence of clinically significant myocardial ischemia 	<ul style="list-style-type: none"> • Diabetes mellitus • Peripheral vascular disease • Carotid artery disease • Abdominal aortic aneurysm • Transient ischemic attacks • 2 or more CHD risk factors with a 10-year risk of CHD >20%. See the 10-year cardiac event risk calculator online at http://hin.nhlbi.nih.gov/atpiii/calculator.asp. 	<ul style="list-style-type: none"> • Male sex • Cigarette smoking • Hypertension (systolic blood pressure \geq140 mmHg or taking antihypertensive medication) • HDL <40 mg/dL (if HDL is \geq60 mg/dL, subtract 1 risk factor) • Patient age \geq45 (men) or \geq55 (women) • Family history of premature CHD in first-degree relatives aged <55 (men) or <65 (women)

In addition, consider the factors below:

History	<ul style="list-style-type: none"> • Factors that contribute to dyslipidemia: <ul style="list-style-type: none"> • Obesity, chronic liver disease, alcohol consumption, high-fat or high-carbohydrate diet, genetic disorders of lipid metabolism, chronic kidney disease, and prothrombotic or pro inflammatory states • Factors that contribute to hypertriglyceridemia: <ul style="list-style-type: none"> • Genetic disorders, obesity, diabetes, alcohol consumption, hypothyroidism, nephritic syndrome, chronic kidney disease • Causes of secondary dyslipidemia, including diabetes, hypothyroidism, nephrotic syndrome, liver diseases • Family history of obesity, diabetes, and lipid abnormalities • Medications <ul style="list-style-type: none"> • ARVs, especially those known to increase cholesterol or TG levels (e.g., ritonavir and ritonavir-boosted PIs, efavirenz, stavudine) • Other medications that may cause lipid abnormalities (e.g., corticosteroids, anabolic steroids, progestins, beta-blockers, thiazide diuretics, quetiapine)
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Physical examination	<ul style="list-style-type: none"> • Blood pressure • Weight, height, and waist circumference (for patients of European descent, abnormal is >40 inches [men] or >35 inches [women]) • Obtain BMI: normally available in the Vitals section of the CPRS Cover Sheet; otherwise BMI = weight (kg)/height (m²); calculator available online, http://www.nhlbi.nih.gov/health/educational/lose_wt/BMI/bmicalc.htm. <ul style="list-style-type: none"> • Underweight: BMI <18.5 • Normal weight: 18.5-24.9 • Overweight: 25-29.9 • Obese: ≥30 • Cardiovascular examination: murmurs, gallops • Stigmata of hyperlipidemia and hypertriglyceridemia: xanthelasma and tendon xanthomas, which are associated with extremely elevated LDL levels; eruptive xanthomas and hepatomegaly, which may be present in the setting of extremely elevated TG levels (chylomicronemia).
Laboratory evaluation	<ul style="list-style-type: none"> • Fasting (8 to 12-hour fast) lipid panel: measured TC, LDL, HDL, and TG levels; calculated non-HDL, and TC/HDL ratio • Fasting glucose; A1c

Assessment Tools

The ACEP guidelines determine whether intervention is needed according to the patient's lipid values and CHD risks, following these 3 steps. **Note that for most patients, LDL is the main indicator of need for lipid-lowering therapy.**

1. Determine CHD risks (above).
2. Determine risk category, LDL goal, and LDL threshold for treatment using **Table 1**.
 - The NCEP also recommends estimating the patient's 10-year risk of MI using the assessment tool derived from the Framingham Heart Study, <http://www.framinghamheartstudy.org/risk-functions/index.php>. Note that this tool does not estimate lifetime risk of MI, which for many patients is substantially higher than their 10-year risk. Intervention to treat lipid abnormalities may be warranted even in patients with a low 10-year risk, to prevent CV events later in life.
 - An alternative estimate of risk of MI or stroke is provided by the ACC/AHA guidelines, <http://www.cvriskcalculator.com>, which introduced a new risk calculator, the Pooled Cohort Risk Assessment Equations that, along with 4 defined groups of patients, is used to determine who should be treated with a statin drug.
3. Assess TG risk level using **Table 2**; determine whether TG-lowering treatment is needed.

Table I. LDL Cholesterol Goals and Thresholds for Treatment*

Risk Category	LDL Goal*	LDL Threshold to Initiate Therapeutic Lifestyle Changes	Consider Drug Therapy
Lower risk: No CHD or CHD equivalents and 0-1 risk factor	<160 mg/dL	≥160 mg/dL	≥190 mg/dL (at 160-189 mg/dL, drug therapy optional)
Moderate risk: No CHD or CHD equivalents; ≥2 risk factors and 10-year estimated risk <10%	<130 mg/dL	≥130 mg/dL	≥160 mg/dL
Moderately high risk: No CHD or CHD equivalents; ≥2 risk factors and 10-year estimated risk 10-20%	<130 mg/dL (optional goal: <100 mg/dL)	≥130 mg/dL	≥130 mg/dL
High risk: CHD or CHD equivalent	<100 mg/dL (optional goal: <70 mg/dL)	≥100 mg/dL	≥100 mg/dL

* Non-HDL cholesterol target levels are 30 mg/dL higher than corresponding LDL cholesterol levels. Adapted from NCEP et al. See **References**.

Other issues:

- Consider drug therapy to decrease LDL (or non-HDL) if TC is >240 mg/dL or HDL cholesterol is <35 mg/dL.
- If TG is >400 mg/dL, the LDL cholesterol calculation is unreliable. Use non-HDL cholesterol as a surrogate target of therapy (non-HDL = TC – HDL); the non-HDL goal is 30 mg/dL higher than the LDL goal.
- If TG is 200-500 mg/dL, LDL is the primary target of initial therapy (see **Table I** for LDL intervention levels); if TG is ≥500 mg/dL, TG may be the initial target of therapy. See below.

Hypertriglyceridemia is associated with CAD risk, but it is unclear whether it is an independent risk factor; hence, indications for treatment are less certain than those for cholesterol abnormalities.

Table 2. Classification of Triglyceride Levels

Risk Category	Triglyceride Measurement	Initiate Therapy
Normal	<150 mg/dL	-
Borderline High	150-199 mg/dL	-
High	200-499 mg/dL	<ul style="list-style-type: none"> • Therapeutic lifestyle changes (Table 3) • Consider drug therapy for those with CHD, CHD equivalents, high risk of CHD
Very High	≥500 mg/dL	<ul style="list-style-type: none"> • Low-fat diet (<15% of caloric intake) • Pharmacologic therapy probably will be required • If severe (>1,000 mg/dL), treat to decrease risk of pancreatitis

Adapted from NCEP et al. See **References** below.

R_x MANAGEMENT

Per the ACEP guidelines, the primary goal of lipid-lowering therapy for most patients is to lower LDL to target levels. The potential benefits of lipid-lowering therapy for patients with HIV infection should be balanced against drug toxicities, as well as the risk of CV mortality relative to HIV-associated mortality. In contrast, the 2013 ACC/AHA guideline Eliminated targets for LDL-C. There are no recommendations for patients with HIV in this document.

- If the TG level is very high, it may have to be reduced before LDL is treated directly. See below.
- Low HDL is not usually a primary target of therapy; data are conflicting as to whether raising HDL confers CV benefits.

A multimodal approach to treatment is important:

- Lifestyle modification
- Lipid-modifying medication
- Changes in ARV medication (or other exacerbating medication), if possible
- Management of associated conditions (e.g., diabetes)

See **Table 1** for LDL levels at which either therapeutic lifestyle changes (see **Table 3**) or drug therapy should be initiated, and for the target goals for LDL cholesterol.

Lifestyle Modification

Lifestyle modification is fundamental to the management of cardiovascular risk and should be initiated in all patients with dyslipidemia. Behavioral changes may

be difficult for patients, but can yield significant results in improving lipid values and reducing CVD risk.

Lifestyle Interventions in HIV Patients (modified from: Raposeiras-Roubin et al.)

Dietary Counseling

- Dietary intervention should not interfere with the dietary requirements necessary for appropriate absorption of antiretroviral drugs (food requirement for atazanavir, darunavir, rilpivirine, cobicistat/elvitegravir).
- Keep caloric intake balanced with energy expenditure.
- Limit intake of saturated fat, cholesterol, and refined carbohydrates.
- Reduce total fat intake to <30% and dietary cholesterol to <300 mg/d.
- Emphasize intake of vegetables, fruit and grain products with fiber.
- Decrease consumption of beverages and foods with added sugar.
- Choose and prepare foods with little or no salt; consume <1500 mg of sodium per day.
- Promote consumption of fish, poultry (without skin) and lean meat.
- Consider 1-week food and beverage diary to discover 'hidden' calories.
- Avoid periods of binge eating and food deprivation ('yo-yo dieting').
- In patients with HIV wasting and dyslipidemia, address wasting first and consider referral to dietitian.
- Weight loss in overweight patients.
- Very low calorie diets are not recommended.
- Restrict alcohol intake restricted to no more than 1 drink/day for women and 2 drinks/day for men (<20-40 g/day).

Exercise Promotion

- Encourage moderate level physical activity (e.g., stair use, cycling or walking to work, cycling, swimming, hiking).
- Emphasize regular moderate-intensity exercise rather than vigorous exercise.
- Achieve cardiovascular fitness (e.g., 30 mins of brisk walking >5 days a week).
- Maintain muscular strength and joint flexibility.

Medication

See **Table 3** and **Characteristics of Lipid-Lowering Medications**, below, for information about lipid-lowering medications. Therapies should be intensified or augmented until lipid targets are met.

Table 3. Suggested Drug Treatments for Lipid Abnormalities

Lipid Abnormality	First Choice	Second Choice	Comments
Isolated high LDL, non-HDL cholesterol	Statin	-	<ul style="list-style-type: none"> • Be aware of possible statin-ARV interactions (see below and Lipid-Lowering Medications, p. 25); use pravastatin, fluvastatin, rosuvastatin, atorvastatin, or pitavastatin for most patients taking PIs or cobicistat. • Patients taking PIs may have increased risk of myopathy. • Start with low statin dosages.
	-	Fibrate (reserve for patients intolerant of other agents who have high LDL, low HDL) Ezetimibe (third choice)*	<ul style="list-style-type: none"> • If incomplete response to statin, consider: <ul style="list-style-type: none"> • Increasing statin dosage • Switching to more potent statin (rosuvastatin or atorvastatin) • Adding ezetimibe • Bile acid sequestrants in general should be avoided unless there are no other options; may interfere with absorption of ARVs and other medications. • Ezetimibe should be used as monotherapy only for patients unable to tolerate statins who do not respond to other agents. • Avoid combining statin and fibrate: increased risk of myopathy. • Niacin is no longer recommended in dyslipidemia management.
Isolated high TG (>500 mg/dL)	N-3 fatty acid Fibrate		<ul style="list-style-type: none"> • Fibrates are most effective in lowering TG. • If response is inadequate, add second agent. • Atorvastatin also lowers TG.

Lipid Abnormality	First Choice	Second Choice	Comments
High LDL + high TG	Statin + N-3 fatty acid	Fibrate	<ul style="list-style-type: none"> • Dual therapy likely to be most effective. • Could start with single agent (e.g., statin) and add second agent if response is inadequate. • Avoid combination of statin and fibrate: increased risk of myopathy.
Isolated low HDL	-	-	<ul style="list-style-type: none"> • Initiate CV exercise.

* See PBM Criteria for Use at <https://www.pbm.va.gov/clinicalguidance/criteriaforuse.asp>.

Characteristics of Lipid-Lowering Medications

Statins (HMG-CoA reductase inhibitors) are the most effective cholesterol reducing drugs with the greatest weight of evidence for cardiovascular benefit.

Statins decrease TC, LDL, and non-HDL cholesterol levels; atorvastatin also decreases TG levels. There is substantial evidence that statins reduce CV events. First-line treatment for most patients with hypercholesterolemia or combined hypercholesterolemia + hypertriglyceridemia. See **Table 4**.

Specifically, atorvastatin and rosuvastatin reduce non-calcified coronary plaque volume and slow progression of carotid intima-media thickness in HIV patients on antiretroviral therapy.

In one observational study, statin use decreased all-cause mortality in HIV patients.

The most common adverse effects associated with statins include myopathy, myalgia, and transaminase elevation (check LFTs one month after initiating, then every three months). Other possible adverse effects include headache, sleep disorders, dyspepsia, nausea, rash, alopecia, erectile dysfunction, gynecomastia, and arthritis. High dose statins may also increase the risk of type 2 diabetes mellitus. However, the use of statins in HIV patients is associated with low rates of adverse events and the discontinuation rate was only 0.12 per 100 person-years. Statins are contraindicated in women who are pregnant or nursing; use with caution in patients with liver disease.

Many statins have significant drug-drug interactions with PIs, cobicistat, and NNRTIs; some combinations are **contraindicated**. See **Lipid-Lowering Medications**, p. 25.

Recommended starting dosages of statins for patients taking protease inhibitors (PI) or cobicistat:

- Pravastatin: 20 mg PO QD -not affected by PI, cobicistat
- Fluvastatin: 20 mg PO QD- not affected by PI, cobicistat
- Pitavastatin: 2 mg PO QD -not affected by PI, cobicistat
- Atorvastatin: 10 mg PO QD – concurrent boosted PI or boosted integrase inhibitor essentially doubles dose; e.g., 10 mg will act like 20 mg
- Rosuvastatin: 5-10 mg PO QD - concurrent boosted PI or boosted integrase inhibitor essentially doubles dose; e.g., 10 mg will act like 20 mg
- **Simvastatin: contraindicated with boosted PI or boosted integrase inhibitor (Genvoya, Stribild)**
- **Lovastatin: contraindicated with boosted PI or boosted integrase inhibitor (Genvoya, Stribild)**

When given concomitantly, statins and fibrates increase the risk of rhabdomyolysis; in general, this combination should be avoided.

Fibrates: Decrease TG and increase HDL; modestly decrease LDL. Gemfibrozil has been shown to reduce risk of CV events (in HIV-uninfected individuals); fenofibrate has not. In one study, clofibrate was associated with increased risk of non-cardiac mortality. An option for initial treatment of isolated hypertriglyceridemia and an alternative treatment for combined hypertriglyceridemia and hypercholesterolemia.

Not metabolized by the cytochrome P450 hepatic enzyme system; no significant drug interactions with ARVs (an exception is lopinavir/ritonavir, which reduces gemfibrozil levels). Contraindicated in severe renal or hepatic disease. Fibrates generally should not be used with statins because of increased risk of myositis. Other possible adverse effects: GI disturbance, gallstones, dizziness. Recommended dosages:

- Fenofibrate: 50-200 mg PO QD
- Gemfibrozil: 600 mg PO BID, 30 minutes before meals

N-3 (omega-3) polyunsaturated fatty acids: Decrease TG levels. May be effective as initial or adjunctive therapy. Limited data suggest CV benefit. Usual dosage 2-6 grams daily. Possible adverse effects: fishy taste, GI disturbance.

Niacin: Increases HDL, decreases both TC and TG. However, niacin does not reduce cardiovascular events, so it is no longer recommended.

Bile acid sequestrants: Generally should be avoided unless no other options; may interfere with the absorption of other drugs (including ARVs), and may increase TG levels.

Ezetimibe: Has not been studied thoroughly in HIV-infected individuals, but appears to be effective in lowering TC and LDL.

- When added to statins, ezetimibe reduces LDL cholesterol levels by an additional 24% and decreases cardiovascular events.

Usually used in combination with statins if LDL is not controlled adequately with a statin. Also potentially useful in statin-intolerant patients. Contraindicated in patients with liver disease.

Switching ARVs

- For patients with CHD or CHD equivalents, try to select ARV medications associated with the lowest risk of dyslipidemia.
 - For patients with dyslipidemia caused by ARV agents, consider discontinuing lipogenic ARVs if safe and effective alternatives exist.
 - For example, substitute atazanavir, an integrase inhibitor, or nevirapine in place of a lipogenic PI (lopinavir-ritonavir or fosamprenavir-ritonavir) or substitute an unboosted PI (e.g., atazanavir) for a ritonavir-boosted PI.
- Replace stavudine with tenofovir preparations (TDF or TAF).
- Before making ARV substitutions, consider the possible effect on HIV virologic control and the potential adverse effects of new ARVs.
- In some cases, antihyperlipidemic agents may still be necessary after ARV substitution.



POTENTIAL ARV INTERACTIONS

Interactions with ARVs: Most PIs inhibit the metabolism of most statins and can significantly increase serum statin levels, thus increasing the risk of toxicity, including rhabdomyolysis. Some combinations are contraindicated. Of the statin drugs, pravastatin is the least affected by most PIs (Darunavir is an exception). Atorvastatin or rosuvastatin, if used, must be initiated cautiously and at lower dose. Efavirenz can induce the metabolism of some statins, causing therapeutically significant decreases in their concentrations. See **Lipid-Lowering Medications**, p. 25, for further information.

Specific effects of Antiretroviral Agents

The effect of antiretroviral drugs on the occurrence CVD of HIV infection is complex. These drugs reduce systemic inflammation, an important factor in CVD development.

In the Strategies for Management of Antiretroviral Therapy (SMART) study, HIV patients with CD4 counts >350 cells per microliter were randomized to receive either continuous or intermittent ARV therapy. The trial was terminated early because those in the intermittent ARV therapy group had greater all-cause mortality, opportunistic infections, and major cardiovascular events. Interleukin 6 and D-dimer levels were significantly elevated in the intermittent treatment group compared with those receiving continuous therapy and these levels were strongly correlated to all-cause mortality.

However, specific antiretroviral agents may also promote atherogenesis by inducing dyslipidemia, insulin resistance, and lipodystrophy, and by affecting LDL particle size. The Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) Study showed a significant increase in acute myocardial infarction (AMI) incidence upon exposure to ARV therapy, with an increased AMI risk of 26% after 6 years of treatment.

Data from the D:A:D study has associated abacavir, didanosine, lopinavir/ritonavir, and fosamprenavir with increased risk of AMI; some other studies have not confirmed this association. Atazanavir is associated with improvements in markers of atherosclerosis, perhaps due to its increase of bilirubin levels, which has anti-atherosclerotic properties. Other widely used HIV drugs that do not impart cardiovascular risk include tenofovir DF, zidovudine, lamivudine, emtricitabine, nevirapine, and efavirenz. Data presented in abstract form by the D:A:D investigators indicate that the risk of cardiovascular disease with darunavir is similar to that with lopinavir/ritonavir. There is insufficient data for darunavir. There is insufficient epidemiologic data to determine the cardiovascular risk profiles of the integrase inhibitors, etravirine, rilpivirine, and maraviroc. However, it has been suggested that maraviroc may have cardioprotective properties, because the CCR5 co-receptor plays a role in the initiation and progression of atherosclerosis. This remains to be demonstrated clinically.

* See PBM Criteria for Use at <https://www.pbm.va.gov/clinicalguidance/criteriaforuse.asp>.

Drug Interactions of Antiretrovirals with other cardiovascular drugs

There are also significant drug-drug interactions of certain antiretroviral agents with antiplatelet, anticoagulant, antiarrhythmic, antianginal, and calcium channel blocking drugs. Protease inhibitors, cobicistat, and NNRTIs strongly interact with warfarin, dabigatran, rivaroxaban, apixaban edoxaban, clopidogrel, prasugrel, and ticagrelor. The antiarrhythmic drugs amiodarone and flecainide, the anti-anginal agents ranolazine and ivabradine, and the calcium channel blocker lercanidipine also have strong interactions with protease inhibitors and cobicistat. See Raposeiras-Roubin et al. for specific **contraindications**.



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Gastroesophageal Reflux Disease (GERD)

KEY POINTS

- Typical symptoms of GERD are heartburn (pyrosis) and regurgitation.
- Less common GERD symptoms (e.g., cough) may mimic other conditions.
- Evaluation of GERD in patients with HIV depends on the stage of infection.
- In patients with a CD4 count of >350 cells/ μ L with typical GERD symptoms, a trial of empiric acid suppression therapy may be undertaken in lieu of other diagnostic testing.
- In patients with more advanced HIV infection, evaluation for OIs affecting the esophagus should be considered, along with empiric GERD therapy.
- Patients with GERD symptoms lasting >5 years and presence of other risk factors should be evaluated by endoscopy for Barrett esophagus because of the increased risk of esophageal carcinoma.
- Patients with alarm symptoms (e.g., unexplained dysphagia or weight loss, hematemesis) should be evaluated by endoscopy for malignancy or other GERD complications.



BACKGROUND

- GERD is defined by the Montreal consensus as symptoms or complications resulting from the reflux of gastric contents into the esophagus. GERD can be further classified as the presence of symptoms without erosions on endoscopic examination (nonerosive disease or NERD) or GERD symptoms with erosions present (ERD).
- The diagnosis of GERD is made using some combination of symptom presentation, objective testing with endoscopy, ambulatory reflux monitoring, and response to antisecretory therapy; although not all are routinely necessary.
- Uncomplicated GERD is characterized by typical symptoms of heartburn, regurgitation, or both.
- Complicated GERD includes Barrett esophagus (see below), esophageal strictures, hemorrhage or perforation, and extraesophageal complica-

Veterans with HIV*

Esophageal disease: 31%
Pancreatic Disease: 4%
Ulcers: 4%

*Veterans in the VA HIV Clinical Case Registry in care in 2017 who had an ICD-9 code corresponding to this condition.

Note: Some medications mentioned in this chapter may not be available on the VHA National Formulary. Consult VA pharmacists for alternatives. Select for the VA National Formulary website, <https://www.pbm.va.gov/NationalFormulary.asp>.

tions such as aspiration, asthma, chronic coughing, chest pain, and laryngopharyngitis.

- Etiology involves movement of gastric juice from the stomach into the esophagus, due to transient lower esophageal sphincter relaxations (tLESRs), hypotensive lower esophageal sphincter (LES), and/or anatomic disruption of the gastroesophageal junction, often associated with a hiatal hernia.
- Symptoms of heartburn are common in Western countries: 25% of the general population is reported to have heartburn at least once a month, 20% has heartburn at least weekly. GERD can have a very negative impact on quality of life. GERD is prevalent among HIV-infected adults, and over half of patients present with symptoms described as frequent and/or moderate-severe in intensity.
- There is no reported association of GERD with HIV infection. For HIV infected patients, however, the differential diagnosis of GERD symptoms includes several HIV-related conditions. See **Partial Differential Diagnosis**, below.
- Esophagitis (esophageal erosions or ulcerations) is seen on esophagogastroduodenoscopy (EGD) or histology in <50% of patients. The majority of patients with GERD symptoms have no evidence of esophagitis on EGD (i.e. NERD).
- The severity and course of symptoms of esophagitis and NERD are similar.
- The condition is often chronic, with remissions and relapses, but usually not progressive. Possible complications include:
 - Esophageal stricture
 - Esophageal ulcers
 - Barrett esophagus
 - Adenocarcinoma
 - Bleeding
 - Perforation
 - Aspiration
- The symptoms and esophageal mucosal injuries caused by GERD usually respond to acid-suppressive treatment, though some complications (e.g., Barrett esophagus) may not improve with treatment.



EVALUATION

- There is no gold standard for diagnosis of GERD. The diagnosis of GERD is made using some combination of symptom presentation, objective testing with endoscopy, ambulatory reflux monitoring, and response to antisecretory therapy; not all are routinely necessary.
- Uncomplicated GERD may be diagnosed by clinical symptoms alone.

- EGD should be considered at presentation for patients with symptoms of complicated GERD (alarm symptoms; see below), and those at risk of Barrett esophagus (see below).
- The differential diagnosis of symptoms referable to the esophagus in patients with HIV depends on the stage of infection.
 - In patients with CD4 counts of <350 cells/mL, the differential diagnosis should include esophageal OIs, such as candidiasis and CMV infection, and endoscopy is warranted.
 - In patients with higher CD4 counts, evaluation should focus on GERD, and on Barrett esophagus and alarm symptoms that suggest malignancy or other conditions (see below); however, the possibility of OIs should be considered as well.
- The American Gastroenterology Association (AGA) recommends screening for Barrett esophagus in patients with multiple risk factors, such as chronic GERD, age 50 years or older, male sex, white race, hiatal hernia, elevated body mass index, intra-abdominal distribution of body fat. The American College of Physicians (ACP) define chronic GERD as and symptoms lasting for >5 years.

Check for Alarm Symptoms:

- Dysphagia
- Odynophagia
- Unexplained weight loss
- GI bleeding (hematemesis, melena, bloody stool)
- Iron deficiency anemia
- Failure to improve with therapy

In HIV-infected patients with relatively high CD4 counts, these increase the odds of malignancy, ulceration, or stricture. If present, refer for immediate evaluation via EGD. Consider starting trial of acid suppression therapy while awaiting further evaluation.

Barrett Esophagus

- Barrett esophagus (BE) is characterized by replacement of the stratified squamous epithelium that normally lines the esophagus with metaplastic columnar epithelium (specialized intestinal metaplasia) associated with chronic GERD. BE can be found in 5 to 15 % of patients who have endoscopy for symptoms of GERD. Most patients are initially seen for symptoms of GERD (heartburn, regurgitation), many are asymptomatic.
- Increases risk of esophageal adenocarcinoma 30-fold compared with GERD alone, with annual incidence of adenocarcinoma of the esophagus of 0.1 to 0.4% per year.

- Unclear whether acid suppression prevents progression of BE or development of adenocarcinoma. However, observational studies suggest that antireflux therapy with proton pump inhibitors might prevent cancer.
- Patients with a history of chronic GERD symptoms (>5 years), with additional multiple risk factors, should be evaluated for BE by EGD.
- The surveillance of BE is determined by the grade of dysplasia. The American College of Gastroenterology recommends the following:
 - For BE patients without dysplasia, endoscopic surveillance should take place at intervals of 3 to 5 years.
 - For patients with indefinite for dysplasia, a repeat endoscopy after optimization of acid suppressive medications for 3–6 months should be performed.
 - For low-grade dysplasia (confirmed by 2nd pathologist), the American Gastroenterological Association (AGA) recommends high dose proton pump inhibitor and repeat EGD by endoscopist experiences in managing dysplasia before considering endotherapy. For high-grade dysplasia (confirmed by 2nd pathologist), endoscopic therapy is indicated.

Risk Factors for GERD (not for BE necessarily)	<ul style="list-style-type: none"> • Obesity: 1.5 to 2-fold risk of GERD, increasing with higher BMI • Pregnancy • Fatty foods • Hiatal hernia • Stress • Medications: beta-blockers, calcium channel blockers, anticholinergics (LES relaxation), • Lifestyle factors: Many of these cause relaxation of the LES, but there is little evidence that GERD results. Associations, if true, appear to be weak, though some patients may be sensitive to these factors. <ul style="list-style-type: none"> • Diet: carbonated sodas, caffeinated beverages, chocolate, saturated fats, peppermint, acidic foods, low fiber • Alcohol use • Smoking
History	<p>History is usually the basis of GERD diagnosis; however:</p> <ul style="list-style-type: none"> • Patients may have atypical symptoms or be asymptomatic. • Severity of symptoms does not predict severity (or presence) of mucosal damage; conversely, severity of esophagitis does not predict severity of symptoms. • There may be great variability in symptoms and findings upon diagnostic testing, and the two may not correlate. • Absence of symptoms does not rule out GERD.

	<p>Symptoms:</p> <ul style="list-style-type: none"> • Heartburn: retrosternal burning pain (because of potential for misunderstanding, it may be helpful to avoid the term “heartburn” and instead ask patients about “a burning feeling rising from the stomach or lower chest up toward the neck”) • Regurgitation: effortless reflux of gastric contents (acid, with or without food); very specific for GERD • Dysphagia • Odynophagia • Symptoms of “extraesophageal” GERD: <ul style="list-style-type: none"> • Cough • Asthma • Chest pain • Hoarseness/voice changes <p>(Note: in the absence of typical symptoms of heartburn or regurgitation, these supralaryngeal symptoms are unlikely to be due to GERD.)</p> <p>Associated factors:</p> <ul style="list-style-type: none"> • Ask about risk factors, above. • Duration of symptoms; patients with a long history of GERD symptoms with additional risk factors should be evaluated for Barrett esophagus (see above). • Symptoms after meals (symptoms after a large or fatty meal: highly specific for GERD) • Symptoms with recumbency (particularly after a meal) • Nocturnal symptoms • Treatments tried and symptom response (improvement with acid-lowering medications supports the diagnosis)
<p>Physical Examination</p>	<ul style="list-style-type: none"> • Performed mostly to evaluate for other causes (infections, asthma, cardiac disease, cancer) • Vital signs; O₂ saturation • Inspection of oropharynx (ulcerations, candidiasis, lesions, masses), neck (nodes, masses), and lungs (wheezes, crackles) <ul style="list-style-type: none"> • Absence of oropharyngeal candidiasis does not exclude esophageal candidiasis. • Abdomen: masses, tenderness • Evaluation for malignancy and infection if history and examination suggest these diagnoses

Diagnostic Tests	<ul style="list-style-type: none"> • Diagnosis of GERD usually is made on the basis of clinical evaluation; in patients with symptoms consistent with GERD, history usually is sufficient to move to a trial of empiric acid-lowering therapy (4-8 weeks) without further evaluation. • Exceptions require immediate and appropriate evaluation: <ul style="list-style-type: none"> • Chest pain (rule out cardiac origin) • Other alarm symptoms (see above) • Other atypical symptoms or findings; high suspicion of an alternative diagnosis • Hematocrit and fecal occult blood testing may be indicated if anemia caused by an upper GI source is suspected. • Helicobacter pylori testing is of no value in evaluation of GERD. If anything, H pylori infection is inversely associated with GERD.
Empiric Proton Pump Inhibitor (PPI) Therapy	<ul style="list-style-type: none"> • Response to acid-lowering therapy (typically PPI therapy) supports a diagnosis of GERD, though studies of correlation show varying results, and symptom improvement may not correlate with findings on EGD or pH monitoring. Sensitivity 78% and specificity 54% for GERD; use of high dosages of PPI may improve sensitivity. • If there is no clinical improvement after 4-8 weeks, consider EGD or other testing as below. <p>(Note that a small number of patients have GERD symptoms that are not related to gastric acid.)</p> <ul style="list-style-type: none"> • Patients who respond to PPI trial should subsequently have a trial of step down to management with H2RAs or no therapy.
EGD	<ul style="list-style-type: none"> • Useful for diagnosing esophagitis and complications (e.g., strictures, Barrett esophagus), but is normal in >50% of patients with symptoms: high specificity (>90%) but low sensitivity (50%) (i.e., normal endoscopy does not exclude GERD). Severity of mucosal injury does not necessarily correlate with symptoms. • The role of EGD in the initial evaluation of patients with uncomplicated GERD is somewhat controversial. The VA Pharmacy Benefits Management (PBM) Services and the American College of Gastroenterology (ACG) propose that a trial of therapy is preferable to EGD for most patients. • Perform EGD as part of initial evaluation for complicated GERD (e.g., if alarm symptoms or other concerning symptoms are present), or if alternative diagnoses are likely (e.g., candidiasis or CMV esophagitis, esophageal cancer, gastritis, and peptic ulcer disease), or if patient is at risk of Barrett esophagus (see above).

	<ul style="list-style-type: none"> • Consider trial of acid-lowering therapy while awaiting EGD; may result in partial [or full] remission of GERD; will improve sensitivity for detection of Barrett esophagus and specificity of a finding of dysplasia. • Perform EGD for patients whose symptoms persist despite therapy; consider for patients with long duration of symptoms (e.g., >5 years) with additional risk factors for Barrett esophagus. • The surveillance interval for Barrett esophagus is determined by the grade of dysplasia at initial EGD. <ul style="list-style-type: none"> • For low-grade dysplasia in the absence of eradication, EGD should be repeated every 6-12 months to exclude higher-grade dysplasia. • For high-grade dysplasia in the absence of eradication, EGD should be repeated within 3 months.
Ambulatory Reflux Monitoring	<ul style="list-style-type: none"> • pH monitoring alone does not detect nonacid reflux. In patients with refractory symptoms despite BID PPI, approximately 10% will have persistent acid reflux, and 40% persistent non-acidic reflux. • Combined pH and multichannel intraluminal impedance monitoring detects both acid and non-acidic reflux. • Consider for patients with persistent symptoms if the EGD is negative for mucosal damage and for those with unusual, extraesophageal, or refractory symptoms. • Can monitor control of reflux in patients on acid-reducing medications (e.g., for patients who are considering surgery).
Barium esophagram	<ul style="list-style-type: none"> • Detects strictures reliably, but is not sensitive or specific for mild erosive or nonerosive disease. • Not sensitive for detection of Barrett esophagus.
Partial Differential Diagnosis	<ul style="list-style-type: none"> • Achalasia • Infectious esophagitis (symptoms usually include odynophagia, dysphagia) <ul style="list-style-type: none"> • Candidiasis • CMV • Herpes simplex virus • Dyspepsia • Peptic ulcer disease • Gastritis • Pill esophagitis • Stricture • Hiatal hernia

- Esophageal dysmotility
- Cancer (esophageal, gastric)
- Gastroparesis
- Coronary artery disease

R_x MANAGEMENT

Acute/Initial Treatment

Goals of therapy:

- Symptom relief
- Healing of esophageal erosions (if present)
- Prevention of complications (data demonstrate reduction in esophageal strictures, but do not clearly show that treatment prevents or slows development of Barrett esophagus or adenocarcinoma.)

As discussed in the **Evaluation** section, empiric acid-suppressing treatment may be initiated on the basis of GERD symptoms. The rate of symptom response to adequate therapy is high (>80%), so patients whose symptoms do not improve should be evaluated for other causes.

Dietary and Lifestyle Modification

Mainstay of management

- Generally aimed at avoiding decreases in LES function, or increases in abdominal pressure or position, which promote reflux of acid above the LES
- Adjunct to acid suppression in all patients; not suitable for sole therapy
- Limited data on efficacy from randomized controlled trials for most measures
- Specific modifications should be based on individual circumstances and identified triggers
 - Weight loss for patients with GERD who are overweight
 - Elevation of the head of the bed in individuals with nocturnal symptoms
 - Avoid assuming a supine position after meals and avoid meals two to three hours before bedtime.
 - Dietary modification should not be routinely recommended to all patients with GERD. However, certain dietary triggers (fatty foods, caffeine, chocolate, spicy foods, food with high fat content, carbonated beverages, peppermint, and alcohol) should be avoided in patients who note a symptom correlation with these foods.
 - Smoking cessation

Medications

Acid-suppressive Agents

Mainstay of medical GERD treatment

- Primary acid-suppressive treatments are PPIs and H2 receptor antagonists (H2RAs).
- For symptom control and healing of esophagitis, the order of efficacy is: high dose PPI >standard-dose PPI >high-dose H2RA >standard dose H2RA
- Patients with erosive esophagitis, frequent symptoms (>2 per week), extra-esophageal symptoms, or a history of failure to respond to H2RAs, should be started on standard-dose PPI rather than an H2RA.
- For patients with NERD, the optimal initial treatment strategy has not been defined. Some authorities prefer to start with PPIs at maximal doses and step down to less-intensive therapy after symptom remission; others prefer to start with less-intensive therapy and step up if symptom relief or esophageal healing is incomplete.
- PPIs and H2RAs may affect serum levels of some ARVs; these drug-drug interactions may influence which type of medication is selected for initial treatment of GERD. See **Potential ARV Interactions**, below.
- Heartburn symptoms relieved in 80%, erosive esophagitis in 90% at 8-12 weeks. Regurgitation relieved in 60%. Atypical chest pain and supralaryngeal symptoms have worse symptom response.

Antacids

- No role as primary therapy (typically, patients have self-treated with antacids without symptom relief).
- Mainly used with mild GERD symptoms that occur less than once a week.
- May be helpful for some patients as supplement to PPI therapy, to be used as needed for breakthrough symptoms.

Prokinetic Agents

- Metoclopramide is the only prokinetic agent available in the United States.
 - Primary effect is on gastric emptying. Weaker effects on increasing LES resting tone, and esophageal peristalsis.
 - Less effective than PPIs; similar to but perhaps less effective than H2RAs

- May cause central nervous system (CNS) adverse effects (e.g., irreversible tardive dyskinesia), QT-prolongation and risk of torsade de pointes.
- Given risks of serious adverse effect, should only be used in patients with comorbid gastroparesis.

Initial Interventions for GERD

PPIs

- Available PPIs have comparable efficacy at equivalent dosages.
- Greater efficacy and more rapid symptom control than H2RAs
- Optimal starting dosage is unclear; some authorities prefer to start with high dosages and step down to less-intensive therapy after symptom remission, others prefer to start at lower dosages and increase treatment intensity if needed.
- **Should be taken a 30-45 minutes before breakfast (and dinner if BID) for optimal effect.**
- Usually well tolerated. Potential adverse effects include GI symptoms (abdominal pain, diarrhea, nausea), headache, rash, and liver toxicity. Other potential adverse effects are described below.
- No dosage adjustment needed for renal impairment.
- May require lower dosage in hepatic impairment; dosage not defined.
- PPIs decrease absorption of drugs with pH-dependent bioavailability, particularly atazanavir and atazanavir-cobicistat (Evotaz) and rilpivirine and its combinations (tenofovir disoproxil fumarate-emtricitabine-rilpivirine (Complera) and tenofovir alafenamide-emtricitabine-rilpivirine (Odefsey). See **Potential ARV Interactions**, below.

Generic Drug Name	Dosage Range	Comments
Dexlansoprazole	30-60 mg QD	If difficulty swallowing, can open capsule and sprinkle contents on applesauce.
Esomeprazole	20-40 mg QD	If difficulty swallowing, can open capsule and sprinkle contents on applesauce.
Lansoprazole	15-30 mg QD or 30 mg BID	If difficulty swallowing, can open capsule and sprinkle contents on applesauce.
Omeprazole	20-40 mg QD or BID	If difficulty swallowing, can open capsule and sprinkle contents on applesauce; immediate-release form contraindicated with hypocalcemia or alkalosis.

Generic Drug Name	Dosage Range	Comments
Pantoprazole	40 mg QD or 40 mg BID	No dosage adjustment needed for hepatic impairment; may cause false positive THC result on urine toxicology screen.
Rabeprazole	20 mg QD or 20 mg BID	Delayed-release tablet

H2RAs

- Less effective than PPIs for acid suppression, relief of symptoms, and healing of esophagitis; approximately 40% of patients achieve symptom relief. Treatment with H2RAs may be adequate for some patients.
- Tachyphylaxis within two to six weeks of initiation of H2RAs limit their use in chronic GERD symptoms. Potential adverse effects vary somewhat according to the specific H2RA. They include cytopenias, rash, GI intolerance, and arrhythmias.
- Dosage adjustment is required for patients with renal insufficiency.
- Cimetidine interacts significantly with many other drugs.
- See **Potential ARV Interactions**, below.

Generic Drug Name	Dosage Range	Comments
Cimetidine	800 mg BID or 800 mg TID	Multiple drug interactions
Famotidine	20 mg BID or 40 mg BID	May decrease ATV absorption.
Nizatidine	150 mg BID or 300 mg BID	May decrease ATV absorption.
Ranitidine	150 mg BID or 150 mg QID or 300mg BID	May decrease ATV absorption; may decrease FPV, LPV, RTV levels.

Antacids

- Role is limited to intermittent use for mild GERD symptom relief.
- Typically contain aluminum hydroxide, magnesium hydroxide, calcium carbonate, sodium bicarbonate, or combinations of these compounds.
- Fast onset of action (less than five minutes), but short half-life (30-60 minutes).
- Liquid formulation is preferable to tablets because of more rapid action.
- Usual dosage is 15-30 mL QID (after meals and at bedtime).
- If tablets are used, they should be thoroughly chewed and followed by full glass of water.

- Antacids combined with alginic acid (e.g., Gaviscon) may be superior to antacids alone, especially for post-prandial symptoms.
- Adverse effects:
 - Antacids containing magnesium: diarrhea
 - Antacids containing aluminum or calcium: constipation
 - Hypophosphatemia with chronic use
 - Magnesium and/or aluminum retention in chronic renal failure
- Multiple drug interactions caused by binding to form insoluble complexes, including PIs and integrase inhibitors. See **Potential ARV Interactions**, below.

Prokinetic Agents

Generic Drug Name	Dosage Range	Comments
Metoclopramide	10-15 mg QID (after meals and at bedtime)	Associated with irreversible tardive dyskinesia, other CNS effects; may consider metoclopramide in patients with comorbid gastroparesis.

Dietary and Lifestyle Modification

Dietary	<ul style="list-style-type: none"> • In most patients, avoiding the following is useful: <ul style="list-style-type: none"> • Carbonated beverages • Voluminous meals • In selected patients, avoiding the following triggers may be useful: <ul style="list-style-type: none"> • Fatty meals • Sweets, including chocolate • Spicy foods/raw onions • Caffeinated beverages • Citrus products/juices
Lifestyle	<ul style="list-style-type: none"> • In most patients, the following are useful: <ul style="list-style-type: none"> • Weight loss • Smoking cessation • Lying on the left side when sleeping • While exercise has been associated with acute worsening of symptoms, chronic use of moderate exercise is associated

	<p>with better symptoms. Moderate exercise is also good for general health.</p> <ul style="list-style-type: none"> • In selected patients, the following may be useful: <ul style="list-style-type: none"> • Avoiding alcohol • Elevating head of bed (for nocturnal symptoms)
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Evaluate Treatment Response (after 4-8 weeks):

Possible responses to treatment	Options for treatment and evaluation
Adequate control of Symptoms	<ul style="list-style-type: none"> • Preferred: Step-down (decrease in intensity) of therapy (e.g., from high-dose PPI to standard-dose PPI, or from PPI to H2RA), with goal of eventually discontinuing therapy, monitor symptoms • Discontinue therapy and monitor symptoms. • Continue current therapy.
Partial Control of Symptoms	<ul style="list-style-type: none"> • Increase intensity of therapy (e.g., to high-dose PPI). • Extend the course of treatment (reevaluate after additional 4-8 weeks). • Refer to GI for further evaluation.
Lack of Response	<ul style="list-style-type: none"> • Increase intensity of therapy. • Consider alternative diagnosis. • Refer to GI for evaluation.

More than 60% of patients respond to adequate therapy. Most authorities recommend that all patients who do not respond to a trial of PPI therapy be referred for further evaluation. In patients with low CD4 counts, consider candidiasis or CMV esophagitis, and other causes.

Relapse of GERD Symptoms:

- Approximately 2/3 of patients with NERD and virtually all patients with erosive esophagitis relapse when acid suppression is discontinued.
- Patients with history of Barrett esophagus and severe erosive esophagitis (Los Angeles grade C or D) should continue acid suppressive therapy indefinitely.
- If patient have recurrent symptoms, restart the medication at the lowest dosage that was effective in controlling the patient's symptoms.
- If relapse occurs on H2RA or low dose PPI, step up therapy is recommended.
- Consider referral for endoscopy if patient has recurrent symptoms despite optimizing acid suppressive therapy, if there are alarm symptoms, or if there is high suspicion of Barrett esophagus.

Chronic GERD Symptoms

- Goals: Suppress symptoms, prevent relapses.
 - Limited data on optimal strategy for long-term acid suppression
 - Chronic maintenance: consider for frequent or rapid relapses, recommended for severe disease (erosive esophagitis, history of strictures, Barrett esophagus).
 - Episodic treatment as needed for relapses: consider for patients with mild GERD.
 - It is rational to use the lowest possible dosage of PPI or H2RA that controls symptoms, but recurrences are common with decreased intensity or discontinuation of medications; efficacy of H2RAs may decline over time due to tachyphylaxis.
 - Chronic acid suppressive therapy with PPIs is associated with prolonged hypochlorhydria, hypergastrinemia, and gastric atrophy. Hypochlorhydria may predispose to infections and malabsorption of micronutrients. Several potential adverse effects may occur with chronic PPI use. However, overall quality of evidence for the occurrence of these adverse effects is low. These potential adverse effects include:
 - *Clostridium difficile* infection (observational studies, low quality of evidence)
 - Hospital Acquired Pneumonia (observational studies and randomly controlled trials, low quality of evidence)
 - Community Acquired Pneumonia (observational studies, with no significant association)
 - Malabsorption (observational studies, low/very low quality of evidence)
 - May decrease serum Mg levels, especially when used with diuretics. The Food and Drug Administration (FDA) recommends obtaining a baseline level and periodic monitoring in patients at risk.
 - May decrease absorption of vitamin B12; use with caution for patients with risk factors for B12 deficiency.
 - Iron malabsorption, particularly in patients requiring oral iron supplements
 - The American Gastroenterology Association (AGA) recommends against routinely screening of bone mineral density and magnesium or vitamin B12 levels and routine supplementing calcium, vitamin B12, or magnesium beyond the recommended dietary allowances.
 - Kidney disease. An association between PPI use and CKD has been suggested, although the mechanism is uncertain (observational

studies, low quality of evidence). AGA also recommends against routinely screening of serum creatinine levels.

- Cardiovascular disease (observational studies, very low quality of evidence).

Surgery and Endoscopic Treatments

Most surgical and endoscopic therapies (e.g., fundoplication) alter LES function, and have variable success. Criteria for selecting patients are not completely defined, but usually include those with large-volume reflux, good responses to medical therapy, or intolerance to medical treatment. Following surgery, a high proportion of patients continue to require acid-lowering medications for control of symptoms. Refer to GI for evaluation.



WHEN TO REFER

Gastroenterology

- Severe symptoms
- Atypical symptoms
- Screening for Barrett esophagus
- Alarm symptoms suggesting malignancy, ulceration, or stricture
- Failure to improve (refractory symptoms, defined as failure to respond to once daily PPI), incomplete response, or relapse on empiric acid-suppression therapy
- Consider for chronic symptoms requiring continuous therapy
- Evaluation for OIs by EGD

Surgery

- Evaluation for fundoplication for:
 - Large-volume reflux
 - Intolerance or failure to medical therapy
 - Complications not responding to high dose PPI
 - Severe esophagitis by endoscopy
 - Benign stricture



POTENTIAL DRUG INTERACTIONS

Acid-lowering medications have interactions with various ARVs. Consult dosing information, as certain combinations require specific dosing strategies, and some are contraindicated. Acid-lowering medications can also have drug interactions

related to effects on cytochrome P450 isoenzymes, e.g., CYP2C19 inhibition by omeprazole; inhibition of CYP1A2, CYP2D6, and CYP3A4 by cimetidine.

PPIs

PPI interactions with ARVs are incompletely studied.

- All PPIs:
 - ↓ atazanavir (ATV) levels (ATV requires an acidic GI environment for absorption); see specific dosing recommendations below
 - ↓ indinavir, unless ritonavir boosted
 - ↑ raltegravir levels
 - ↓ rilpivirine (contraindicated)
- Omeprazole (in addition to all PPIs, above):
 - ↓ nelfinavir
 - ↑ etravirine (AUC increased 41% by CYP2C19 inhibition), saquinavir

H2RAs

- All H2RAs:
 - ↓ ATV levels; see specific dosing recommendations below
 - May ↑ RAL levels
 - For rilpivirine (or Complera or Odefsey), the H2RA must be given 12-hours before or 4-hrs after the rilpivirine dose
- Cimetidine (in addition to all H2RAs, above):
 - ↓ nevirapine levels; dosage adjustment not established
 - May ↑ fosamprenavir levels; consider alternative agents
 - May ↓ darunavir levels
- Ranitidine
 - May ↓ fosamprenavir and lopinavir/ritonavir levels; dosage adjustments not established

Antacids

- Maalox, Mylanta, Tums, milk of magnesia, others
 - May ↓ levels of ATV, fosamprenavir, tipranavir, rilpivirine (or Complera or Odefsey); separate dosing by 2 hours
- Calcium (e.g., Tums, Mylanta)
 - May bind integrase inhibitors and interfere with their activity (until further information is available, separate dosing by at least 2 hours)

Dosage Recommendations: ATV with PPIs or H2RAs

	ARV-Naive Patients	ARV-Experienced Patients
PPI	<ul style="list-style-type: none"> • ATV/ritonavir 300/100 mg QD; PPI dosage not to exceed the equivalent of omeprazole. 20 mg QD, with the PPI to be taken approximately 12 hours before ATV/r. • Unboosted ATV is not recommended. 	<ul style="list-style-type: none"> • PPIs are not recommended.
H2RA	<ul style="list-style-type: none"> • ATV/ritonavir 300/100 mg QD; H2RA dosage not to exceed the equivalent of famotidine 40 mg BID; give ATV/r with the H2RA and/or ≥ 10 hours after the H2RA. • Unboosted ATV is not recommended; if used with H2RA, H2RA should not exceed the equivalent of famotidine 20 mg per dose or daily total of 40 mg; give ≥ 2 hours after and/or ≥ 10 hours before ATV/r. 	<ul style="list-style-type: none"> • ATV/r 300/100 mg QD; H2RA dosage not to exceed the equivalent of famotidine 20 mg BID; give ATV/r with the H2RA and/or ≥ 10 hours after the H2RA. • If TDF is used in the regimen, give ATV/r 400/100 mg QD. Administer H2RA as described above. • Unboosted ATV is not recommended.

Source: Reyataz package label



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KEY POINTS

- Hepatitis B is transmitted perinatally and by unprotected sexual intercourse and intravenous drug use.
- Hepatitis B can present acutely or chronically. Infection with HBV or immunity to HBV is associated with characteristic patterns of hepatitis B antigens and antibodies which aid in diagnosing the disease stage as well as monitoring.
- Agents active against hepatitis B include pegylated interferon alpha-2a, lamivudine, emtricitabine, entecavir, adefovir, tenofovir DF, and tenofovir AF. Drugs active against both HIV and hepatitis B include lamivudine, emtricitabine, and tenofovir.
- About 5% to 10% of people with HIV in the U.S.A. are coinfecting with HBV. The progression of chronic HBV to cirrhosis, end-stage liver disease, or HCC is more rapid in patients with HBV/HIV coinfection than in persons with HBV infection alone. There is an increased risk of progression to AIDS in patients with HBV coinfection.
- Patients with HIV/HBV coinfection generally use TDF or TAF with lamivudine or emtricitabine as the backbone of the ARV regimen. Emtricitabine or lamivudine should not be used as monotherapy to treat HBV.
- The HBV vaccine is effective in preventing HBV infection. The standard 3-dose vaccine series induces protective antibody concentrations in >95% of healthy persons. However, there is a blunted response to HBV vaccination in immunocompromised adults. Response rates to the vaccine in patients with HIV can be increased by doubling the vaccine dose or giving a 4-part series.
- Ultrasonography (US) is the main tool for HCC surveillance in patients with HBV with or without cirrhosis. Patients with a positive screening US should receive a dynamic CT or dynamic MRI.



BACKGROUND

The hepatitis B virus (HBV) is the leading cause of chronic hepatitis, cirrhosis, and hepatocellular carcinoma (HCC) worldwide, with an estimated 257 million people currently infected. In 2015, hepatitis B virus (HBV) resulted in 887,000 deaths, mainly from cirrhosis and HCC. During the acute phase, the spectrum of disease ranges from asymptomatic hepatitis to icteric hepatitis, including fulminant hepatitis. Once chronic infection is established, the disease may progress from an asymptomatic, carrier state to progressive liver disease, cirrhosis, and HCC. Antivirals are available to control viral replication; however, a cure is not consistently possible with current agents. A highly effective vaccine is also available.

Note: Some medications mentioned in this chapter may not be available on the VHA National Formulary (<https://www.pbm.va.gov/NationalFormulary.asp>). Consult VA pharmacists for alternatives.

Approximately 5% of the world's population is chronically infected with HBV. The prevalence of chronic HBV varies widely, from 0.01% to 2% in the low-prevalence areas (U.K., U.S.A., Canada, Western Europe, Australia, and New Zealand), to 2% to 7% in areas with intermediate prevalence (Japan, Central Asia, Israel, Eastern and Southern Europe, Central America, and South America), to >8% in high prevalence areas (Southeast Asia, China, Middle East, Haiti and Dominican Republic, and Africa). The epidemiology of HBV is changing with the employment of universal vaccination programs adopted by many countries. In the U.S.A., the estimated number of new symptomatic infections per year was more than 10 per 100,000 in the mid-1980s which has decreased to about 1.6 per 100,000 in 2006. Among American military Veterans in 2016, the prevalence of active hepatitis B was 0.84%, compared to 0.3 to 0.5% for overall prevalence in the U.S.A. The rate of hepatitis B infection is 2.5 times higher in Veterans who are homeless.

Pathogenesis and Natural History of Disease

The natural history of hepatitis B infection consists of four phases. The first phase, the immunotolerant phase, is characterized by limited immune response. There is minimal elevation of serum aminotransferases and minimal liver inflammation despite circulating HBsAg, HBeAg, and high levels of HBV DNA. The second phase is the immunoactive phase, where there is a reduction in HBV DNA levels and an increase in immune response, accompanied by increased aminotransferases and liver inflammation. This is usually the period of symptomatic HBV. During the third phase, which does not occur in all infected individuals, conversion from HBe antigenemia to anti-HBe occurs, which can be accompanied by an increase in aminotransferases above baseline, suggesting a greater immune control of the virus than in the second phase. Following the third phase, one of three outcomes occurs. The most common is a decrease in viral replication and reduction in ALT with low or undetectable HBV DNA and is referred to as inactive hepatitis B. Some individuals will also clear HBsAg, although this is unusual, occurring in less than 1% of patients per year in adults. The second outcome is seroreversion to HBeAg positivity and return to the immunoactive (second) phase, which occurs 10% to 40% of the time. The third outcome is that patients remain with high levels of HBV DNA and elevations of ALT but remain HBeAg-negative, which occurs about 20% of the time.

Routes of Transmission

Parenteral or mucosal exposure to infected blood are the main routes of transmission, with HBV being 100 times more efficiently transmitted compared with HIV after needle stick exposure. HBV is also found in other body fluids, including semen, saliva, cervical secretions, and tears. It can survive up to 7 days on environmental surfaces. HBV is spread by percutaneous or mucosal exposure to infected blood and body fluids. Sexual transmission of HBV can occur, particularly in unvaccinated MSM and heterosexuals with multiple partners. Infection in

adulthood leads to chronic hepatitis in less than 5% of cases. Transmission of the virus may also occur through the reuse of needles and syringes either in health-care settings or among persons who inject drugs. In addition, infection can occur during medical, surgical, and dental procedures, through tattooing, or through the use of contaminated razors and similar objects. Perinatal transmission is the predominant mode in high-prevalence areas, whereas horizontal transmission, particularly in early childhood, accounts for most cases of chronic HBV infection in intermediate prevalence areas. Unprotected sexual intercourse and intravenous drug use are the major routes of contagion in low-prevalence areas.

Clinical Presentation

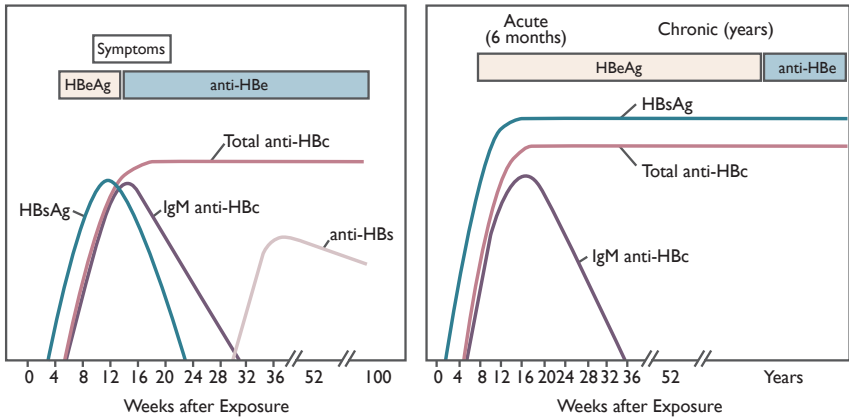
Clinical manifestations of HBV infection occur in both acute and chronic forms. The acute phase, can vary from subclinical or anicteric hepatitis to icteric hepatitis and fulminant hepatitis. During the chronic phase, presentations can range from an asymptomatic carrier state to cirrhosis and hepatocellular carcinoma (HCC). Extrahepatic manifestations can also occur during both acute and chronic infection.

Acute Hepatitis B

Incubation period for acute infection is 1-4 months. Symptoms consist of flu-like syndrome with malaise, fatigue, anorexia, nausea, vomiting, and right upper quadrant discomfort. Serum sickness-like manifestations may occur before the onset of jaundice. Signs of acute hepatitis B include jaundice and tender hepatomegaly. The acute illness may be more severe in the setting of other coinfections, such as hepatitis D, or with underlying liver disease such as alcoholic liver disease. Lab testing during the acute phase reveal elevated ALT and AST (ALT>AST), with levels up to 1000 to 2000 IU/L. The prothrombin time (PT) is the best indicator of prognosis, with a high PT indicative of fulminant liver failure. Among patients who recover, normalization of serum aminotransferases usually occurs within 1 to 4 months. Persistent elevation of ALT for >6 months indicates chronic hepatitis. Chronic hepatitis develops in less than 5% of adults, 10% to 25% of young children, and 80% to 90% of infants after acute HBV infection. Patients who recover from acute hepatitis B are probably not truly cured of infection because a significant number of patients will have detectable HBV DNA years after clinical recovery. They generally have lifelong protection from disease unless there is significant immunosuppression with loss of protective immune responses, such as in the setting of HIV, chemotherapy, or bone marrow transplant.

Fulminant HBV is rare, occurring in only 0.1% to 0.5% of patients. Patients typically present with rapidly progressive acute hepatitis, with less than 28 days from the time of symptom onset, accompanied by signs of liver failure, such as coagulopathy, encephalopathy, and cerebral edema.

Figure 1. Typical courses of (A) acute and (B) chronic hepatitis B.



Chronic Hepatitis B

Chronic hepatitis B is defined by at least 6 months of persistent HBV antigenemia. Symptoms include fatigue, nausea, right upper quadrant tenderness, anorexia, myalgias, and arthralgias. The exam may be normal or there may be hepatomegaly or signs of cirrhosis (jaundice, splenomegaly, ascites, encephalopathy, lower extremity edema). Labs may show a normal ALT and AST, or have mild to moderate elevations. Patients have markers of viral replication, including HBsAg and often HBeAg or HBV DNA. During flares of disease activity there may be marked elevations in the serum aminotransferases to >20 times normal. IgM anti-HBc may increase during these flares leading to a false diagnosis of acute hepatitis. Repeated episodes of flares are risk factors for hepatocellular carcinoma (HCC). A histopathologic characteristic of chronic hepatitis B is the presence of ground glass hepatocytes, thought to be due to the accumulation of HBsAg within the endoplasmic reticulum.

Occult Hepatitis B

Isolated HBV core antibody (HBcAb) in the absence of HBsAg and HBsAb occurs in up to 34%, 50%, and 59% of patients who are HIV/HCV-coinfected, HCV mono-infected, and HIV mono-infected, respectively. Isolated HBcAb can indicate: (1) occult HBV viremia (HBV viremia in the absence of HBsAg); (2) resolved infection with low titers of HBsAb; (3) a window period during acute infection; or (4) a false positive result. In the large Veterans Aging Cohort Study group, 12% and 37% of patients with HIV and HIV/HCV, respectively, had isolated HBcAb positivity. Advanced hepatic fibrosis with isolated HBcAb positivity was observed in patients who are HIV/HCV-coinfected, but not in HIV mono-infection.

Hepatitis D

Hepatitis Delta virus (HDV) is an incomplete human RNA virus that requires chronic HBV infection for replication. Infection of persons with chronic HBV with HDV results in chronic delta hepatitis, which is associated with accelerated fibrosis and increased risk of HCC relative to HBV infection alone. The prevalence of chronic delta hepatitis in the U.S.A. is rising due to increased sexual transmission and IV drug abuse. Hepatitis D infection is underdiagnosed. In a VA study from 2015, only 7.8% of patients with HBsAg positivity were tested for HDV, and 3.6% of these were HDV seropositive. The prevalence of HCV and HIV coinfection and cirrhosis was higher among HDV-positive patients versus HDV-negative individuals. Testing for HDV is recommended for patients with hepatitis B with a known history of IV drug abuse and patients with coinfection (HIV/HBV, HCV/HBV, HIV/HCV/HBV).

Extrahepatic manifestations of Hepatitis B

Extrahepatic manifestations occur in about 20% of patients with acute and chronic HBV. Acute hepatitis may present as a serum sickness–like illness with fever, skin rash, arthralgias, and polyarthritides, typically occurring just before the onset and subsiding with the development of jaundice. Other manifestations include rash, neuropathies, myalgias, arthralgias, Sjögren’s syndrome, glomerulonephritis, uveitis, and Raynaud’s syndrome. Autoantibodies may also be present, including cryoglobulin and rheumatoid factor. Polyarteritis nodosa is a rare complication of chronic hepatitis B, which usually manifests within the first six months of infection.



EVALUATION

Infection with HBV or immunity to HBV is associated with characteristic patterns of HBV antigens and antibodies which aid in diagnosing the disease stage as well as monitoring (**Table I**).

Table I. Characteristic pattern of antigens and antibodies in hepatitis B infection and immunity

Test	Acute hepatitis B	Immunity through infection	Immunity through vaccination	Active chronic hepatitis B	Inactive chronic hepatitis B
HBsAg	+	-	-	+	+
Anti-HBs	-	+	+	-	-
HBeAg	+	-	-	±	-

Anti-HBe	-	±	-	±	+
Anti-HBc	+	+	-	+	+
Anti-HBc IgM	+	-	-	-	-
HBV DNA	+	-	-	+	+
					(low)
ALT	Elevated	Normal	Normal	Elevated	Normal

HBsAg is the serologic hallmark of HBV infection and is the first serum marker to appear after acute infection (1 to 10 weeks after exposure). In patients who recover, HBsAg becomes undetectable after 4 to 6 months, followed by development of anti-HBs which persists for life, conferring long lasting immunity. During acute infection, anti-HBc antibody is detectable at the time symptoms appear (9 to 21 weeks after exposure) and is predominantly IgM class. It can be the sole marker of HBV infection during the window period between the disappearance of HBsAg and the appearance of anti-HBs. IgG anti-HBc persists and signifies natural infection. The diagnosis of chronic HBV is based on the persistence of HBsAg for more than 6 months. Additional tests for HBV replication, such as HBeAg and serum HBV DNA, should be performed in those with chronic hepatitis B to further classify the disease and to determine the need for treatment. A dose-response relationship exists between the HBV DNA level and the risk of developing cirrhosis and HCC.

Management of Hepatitis B

The initial evaluation of persons with hepatitis B virus (HBV) should include a history and physical exam, with emphasis on risk factors for coinfection, alcohol use, and family history of HBV infection and hepatocellular carcinoma (HCC). Laboratory tests should include assessment of liver disease activity and function, markers of HBV replication, and tests for coinfection with hepatitis C virus (HCV), hepatitis delta virus (HDV), or human immunodeficiency virus (HIV) in those at risk (**Table 2**).

Table 2. Initial Evaluation of the HBsAg-Positive Patient

Patient	History/Exam	Routine Lab Tests	Serology/Virology Testing	Imaging/Staging Studies
All	<ul style="list-style-type: none"> Signs/symptoms of cirrhosis Alcohol use Family History 	<ul style="list-style-type: none"> CBC AST/ALT Bilirubin Alkaline 	<ul style="list-style-type: none"> HBeAg/anti-HBeAg HBV viral load 	<ul style="list-style-type: none"> Abdominal ultrasonography^{c,d} Elastography^c Serum fibrosis panel^{c,e}

	HCC • Immunization status	phosphatase	• Anti-HAV Ab	
Select	-	<ul style="list-style-type: none"> • Tests to evaluate for other causes of chronic liver disease^a • Alpha fetoprotein^b 	<ul style="list-style-type: none"> • Anti-HDV • Anti-HCV • Anti-HIV • HBV genotype 	<ul style="list-style-type: none"> • Dynamic Liver CT^{c,d} • Liver biopsy

^aAutoimmune hepatitis, hemochromatosis, non-alcoholic steatohepatitis, Wilson's disease, alpha 1-antitrypsin deficiency, biliary tract diseases, others. ^bMarker of HCC. ^cTo assess for cirrhosis. ^dTo assess for HCC. ^eIncludes APRI score, Fib-4, FibroTest, others.

Chronic Hepatitis B

The goals of antiviral therapy in HBV are reduction of the morbidity and mortality due to liver disease. Various end points have been used as surrogates to define response to treatment in clinical trials, including normalization of serum aminotransferases (biochemical response), improvement in liver histology (histologic responses), achieving an undetectable serum HBV DNA (virologic response), and loss of HBeAg with or without the development of anti-HBe (serologic response). For patients who are HBeAg-positive and achieve seroconversion to anti-HBe, therapy is usually continued for 6-12 months thereafter. For those who do not seroconvert on treatment or who are HBeAg-negative, therapy is generally continued indefinitely.

Approved Antiviral Therapies

There are five agents approved for the treatment of adults with chronic HBV in the United States (**Table 3**). Side effects are more frequent with interferon (IFN) therapy than with nucleos(t)ide analogs (NAs) therapy. Overall, the NAs have an excellent safety profile across a wide spectrum of persons with HBV, including those with decompensated cirrhosis and transplant recipients.

Table 3. FDA Approved Drugs for the Treatment of Hepatitis B, 2017

Drug	Adult Dose	Pregnancy Category	Potential Side-effects	Monitor on Treatment
Peg-IFN alpha-2a	180 mcg/ weekly	C	Flu-like symptoms, fatigue, mood change, cytopenias, autoimmune disorders	CBC every 1-3 months TSH every 3 months Clinical for autoimmune, ischemic, neuropsychiatric, Infectious complications
Lamivudine	100 mg daily	C	Pancreatitis Lactic acidosis	Lipase if clinical concern Lactic acid if clinical concern
Entecavir	0.5 to 1 mg daily	C	Lactic acidosis	Lactic acid if clinical concern
Adefovir	10 mg daily	C	Acute renal failure Fanconi Syndrome Diabetes insipidus Lactic acidosis	Creatinine clearance at baseline Creatinine clearance, phosphorus, and urine protein at least annually DEXA bone density scan for patients with history of a fracture or with risk factors for osteopenia
Tenofovir disoproxil fumarate	300 mg daily	B	Nephropathy Fanconi Syndrome Diabetes insipidus Lactic acidosis Osteomalacia	Creatinine clearance at baseline Creatinine clearance, phosphorus, and urine protein at least annually DEXA bone density scan for patients with history of a fracture or with risk factors for osteopenia
Tenofovir alafenamide	30 mg Daily	B	Lactic Acidosis	As above, but less risk for bone and renal toxicity

Current recommendations are to treat all cirrhotic patients and non-cirrhotic patients with detectable HBV DNA (either HBeAg-positive with a HBV DNA >20,000 IU/mL, or, in the case of HBeAg-negative disease, with HBV DNA >2000 IU/mL) and liver disease (serum aminotransferases >two times the upper limit of normal (30 U/L for men and 19 U/L for women) or moderate-to-severe necroinflammation on biopsy) (Table 4).

Table 4. Treatment Strategy Based on HBe Antigen

HBeAg	HBV DNA	ALT	Treatment Strategy
+	>20,000 IU/mL	<2 times LN	<ul style="list-style-type: none"> • Observe • Consider liver biopsy if age >40, ALT >1 but <2 times ULN, family history HCC, HIV-positive; treat if moderate-to-severe inflammation or fibrosis
+	>20,000 IU/mL	>2 times ULN	<ul style="list-style-type: none"> • Observe 3-6 months for spontaneous HBeAg seroconversion • Treat with PEG IFN-alfa (48 weeks) or nucleos(t)ide (indefinite in most; min 3-6 months after HBeAg seroconversion)
-	>20,000 IU/mL	>2 times ULN	<ul style="list-style-type: none"> • Treatment with nucleos(t)ide (end-point not defined, likely indefinite); • PEG IFN-alfa (48 week) second line
-	>2000 IU/mL	1 to <2 times ULN	<ul style="list-style-type: none"> • Consider liver biopsy and treatment if moderate to severe inflammation or fibrosis
-	>2000 IU/mL	<ULN	<ul style="list-style-type: none"> • Observe; treat with HBV DNA or ALT increases
±	+	Cirrhosis	<ul style="list-style-type: none"> • Compensated; treat with nucleos(t)ide if HBV viral load detectable • Decompensated; treat with nucleos(t)ide; consider liver transplant
±	-	Cirrhosis	<ul style="list-style-type: none"> • Compensated; observe • Decompensated; consider liver transplant

Treatment in acute hepatitis B is generally supportive.

Prevention of Hepatitis B Infection

The HBV vaccine is effective in preventing HBV infection and its complications. The efficacy of the vaccine is due to the production of anti-HBs antibodies and the induction of memory T-cells. An anti-HBs concentration of ≥ 10 IU/L measured 1–3 months after the last dose of the vaccination series is a reliable marker of protection against infection. The standard 3-dose vaccine series induces protective antibody concentrations in >95% of healthy persons, which persists for at least 2 decades in the majority of immunocompetent individuals. However, there is a blunted response to HBV vaccination in immunocompromised adults, including patients with HIV. In patients with HIV, using the standard

dose of 20 mcg and the standard schedule of 0, 1 and 6 months, the efficacy of HBV immunization ranges from 34 to 89%.

Using a 40 mcg dose and the standard three-part dosing, efficacy of the HBV vaccine in patients with HIV ranged from 47 to 64%. Other studies evaluating a 40 mcg dose given at 0, 1, 2 and 6 months found a protective response in 89 to 91% of HIV-infected subjects. Patients that fail to mount a protective immune response after the initial immunization, a rescue series generated a 67 to 70% protective response. A protective response to HBV vaccination is more likely in patients with a low or undetectable HIV viral load and higher CD4 counts. Other factors associated with reduced vaccine response are older age, alcohol and tobacco abuse, and African American race. Patients with HIV may also fail to maintain long-lasting protective titers after HBV immunization. In one study, after a median follow-up of 43 months, 73% of 152 participants maintained protective levels of anti-HBs. In this case, HIV viral load suppression at the time of immunization was associated with persistent protective levels of anti-HBs.

Despite the lower response in patients with HIV with low CD4 counts, HBV vaccination should not be deferred until the CD4 count is higher. Anti-HBs levels should be obtained one month after completion of the vaccine series to assess vaccine response. In patients with HIV with an ongoing risk for HBV acquisition, yearly assessment of HBs levels are recommended.

Prevention of Perinatal Transmission

In women with chronic HBV infection, the risk of transmission of HBV infection to their child is high and varies according to HBeAg status of mothers, from 12% for HBeAg-negative/anti-HBe-positive mothers, to 25% for HBeAg-negative/anti-HBe-negative mothers, to 70% to 90% for HBeAg-positive mothers. Maternal serum HBV viral loads correlate with transmission risk. It is recommended that all neonates born to mothers with chronic hepatitis B receive hepatitis B immunoglobulin (HBIG) 30 IU at birth and hepatitis B vaccine within 12 hours of birth followed by re-immunization at 1 and 6 months, which together are 85% to 95% effective in preventing perinatal HBV infection.

Post-Exposure Prophylaxis

Post-exposure prophylaxis with HBIG and vaccine is recommended for nonimmune individuals who have percutaneous, sexual contact, ocular, or mucous membrane exposure to blood, including human bites that penetrate the skin, where the source is known to be at high risk of being HBsAg-positive. The first dose of 0.06 mL/kg should be administered as soon as possible, although there is a window period of up to 24 hours. The first vaccine dose should be given at the same time, although in a different site, followed by the remainder of the series. For individuals with a history of HBV vaccination but who do not have documentation of adequate titers of anti-HBs, recommendations are to administer both HBIG and a vaccine booster dose pending documentation of adequate anti-HBs

levels. Individuals who fail to respond to the vaccine series require two doses of HBIG one month apart.

Hepatitis B/HIV Coinfection and Considerations for Antiretroviral Use

About 5% to 10% of people with HIV in the U.S.A. are coinfecting with HBV. The progression of chronic HBV to cirrhosis, end-stage liver disease, or HCC is more rapid in patients with HBV/HIV coinfection than in persons with HBV infection alone. In patients with HBV/HIV coinfection, (TAF or TDF) plus (3TC or FTC) can be considered part of the ARV regimen; entecavir has weak anti-HIV activity and must not be considered part of an ARV regimen. In addition, TDF is fully active for the treatment of persons with known or suspected 3TC-resistant HBV infection, whereas 3TC resistance compromises the activity of entecavir against HBV.

Recommended Therapy in Patients Who are Coinfected with HBV/HIV

The combination of (TAF or TDF) plus (3TC or FTC) is the NRTI backbone of choice for an ARV regimen in HIV/HBV coinfection. TAF/FTC-containing regimens are not recommended for use with creatinine clearance <30 mL/min. Data from one elvitegravir/cobicistat/TAF/FTC switch study indicate that patients with HBV/HIV coinfection can switch to TAF/FTC-containing regimens with a reduction in renal and bone toxicity while maintaining HBV suppression.

Alternative Therapy to Patients Who are Coinfected with TDF and TAF

If TDF or TAF cannot safely be used, entecavir should be used in addition to a fully suppressive ARV regimen. In persons with known or suspected 3TC-resistant HBV infection, the recommended entecavir dose is 1 mg/day. However, entecavir resistance may emerge rapidly in patients with 3TC-resistant HBV infection. Thus, entecavir should be used with caution with frequent monitoring (about every 3 months) of the HBV DNA level to detect viral breakthrough.

Pegylated interferon alfa monotherapy for up to 48 weeks may also be considered in some patients with HBV/HIV coinfection, but data are limited. Peg interferon alfa should not be used in patients with decompensated cirrhosis.

HBV Drugs Not Recommended in HBV/HIV Coinfection

The use of adefovir or telbivudine for patients with HBV/HIV coinfection is not recommended.

Changing Antiretroviral Therapy

- Need to discontinue ARV medications active against HBV: The patient's clinical course should be monitored with frequent liver function tests. The use of entecavir to prevent flares can be considered, especially in patients with marginal hepatic reserve, i.e., cirrhotics. Entecavir should only be used with a fully suppressive ARV regimen.
- Need to change ARV therapy because of HIV resistance: If the patient has adequate HBV suppression, the ARV drugs active against HBV should be continued for HBV treatment in combination with other ARV agents that effectively suppress HIV.

Hepatocellular Cancer Risk in Hepatitis B

In a study of U.S. military Veterans with hepatitis B, hepatocellular carcinoma (HCC) risk was twice as high in Asians/Pacific Islanders, as compared to Caucasians and African Americans. In the same study, hepatitis B patients with cirrhosis had a 3.7-fold higher risk of HCC than those without cirrhosis. Even without cirrhosis, the annual incidence of HCC was >0.2% for all HBV-infected patients older than 40 years with high ALT levels, regardless of race. For cirrhotic patients with HBV, the 10-year incidence of HCC was 2.2-times higher in patients without virologic remission than those with suppressed HBV viral load.

Ultrasonography (US) is the main tool for HCC surveillance in HBV patients with or without cirrhosis, with a sensitivity of 65-80% and a specificity of 85-90%. However, the sensitivity of US is decreased in obese patients. A randomized controlled trial of over 18,000 patients with HBV with or without cirrhosis, found that biannual screening decreased HCC-related mortality by 37%. There is disagreement between different guideline recommendations regarding the utility of measuring alpha fetoprotein (AFP), due to its low sensitivity for the detection of HCC in its early stages. AFP levels in combination with US detect 6-8% of cases not visualized by US, but the false-positive rate is also increased by 7.9%.

Patients with a positive screening US or AFP determination should receive a dynamic CT or dynamic MRI; HCC has characteristic findings in these studies (hypervascularity in the arterial phase and washout in the delayed phase). Current guidelines for the diagnosis of HCC do not require biopsy to prove the diagnosis of HCC; lesions >2 cm on MRI or CT scans, along with AFP elevated more than 400 ng/mL or rising with sequential measurements, do not require histologic confirmation.



WHEN TO REFER

- Refer adults who develop decompensated liver disease to a hepatologist (symptoms of decompensated liver disease include ascites, encephalopathy and gastrointestinal hemorrhage).
- Refer pregnant women who are HBsAg-positive to a hepatologist or infectious disease specialist with an interest in hepatology for assessment within 6 weeks of receiving the screening test result and to allow treatment in the third trimester.
- Refer patients with liver lesions suspicious for HCC to a hepatologist.



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KEY POINTS

- In the era of improved survival from ARV therapy, chronic liver disease has become a leading cause of morbidity and mortality in patients with HIV.
- Because of shared modes of transmission (IVDU, MSM), hepatitis C virus (HCV) infection is particularly common among patients with HIV.
- The development of direct-acting antivirals (DAAs) for HCV has revolutionized HCV treatment, allowing for high cure rates with minimal side effects.
- Because HIV infection accelerates the progression of HCV related liver disease, all patients with HIV/HCV co-infection should be evaluated for direct-acting antivirals.
- Current substance use (alcohol, illicit drugs or marijuana) or participation in opioid substitution treatment should not be an exclusion from evaluation for HCV treatment.

Note: Current information on VHA policy, guidelines, and tools related to liver disease can be found on the VA Viral Hepatitis website, <https://www.hepatitis.va.gov>.



BACKGROUND

Chronic infection with HCV is the leading cause of liver disease and liver transplantation in the United States. The Department of Veterans Affairs is the largest provider of medical care to persons with HCV in the nation. Approximately 30-40 % of Veterans with HIV are co-infected with HCV, <https://www.hepatitis.va.gov/>.

Given the high rates of infection with both viruses, all patients newly diagnosed with HIV infection should also be screened for HCV. Routine testing for HCV infection is recommended for groups with continued risk.

The symptoms of acute hepatitis C infection, if present, are often mild. Chronic infection develops in 75-80% of cases. Chronic HCV infection is usually asymptomatic for many years. Long-term liver complications of HCV infection include cirrhosis, end-stage liver disease (ESLD), and hepatocellular carcinoma (HCC). Co-infection with HIV results in a faster progression to liver complications, and more than triples the risk of liver failure and liver-related death.

Successful antiviral treatment of chronic HCV infection decreases the risk of disease progression and death. New direct-acting antiviral (DAA) agents require shorter durations of therapy, have favorable side effect profiles, and yield sustained virologic response (SVR) or cure rates of greater than 90% in clinical trials, similar to HCV mono-infected patients. Obtaining an SVR is associated with reduction in the risk of cirrhosis, liver cancer, liver failure or death.

Note: Some medications mentioned in this chapter may not be available on the VHA National Formulary (<https://www.pbm.va.gov/NationalFormulary.asp>). Consult VA pharmacists for alternatives.



SCREENING

HCV Ab with reflex PCR testing is recommended for HIV-seropositive patient at entry into care.

Annual HCV Ab with reflex PCR testing is recommended for persons at ongoing risk including but not limited to injection drug use, regular condomless sex with partners of unknown sexually transmitted infection (STI) status.

Note:

All patients who have active hepatitis C as determined by a detectable HCV RNA viral load need to be referred for treatment, unless they have a condition associated with poor short-term survival.



EVALUATION

- Clinicians should review the hepatitis C test results and confirm the patient has chronic hepatitis C virus (HCV) infection as determined by a measurable HCV RNA viral load. Resolved HCV infection would be indicated by a negative HCV RNA viral load.
- HIV/HCV co-infected patients should be evaluated for clinical, biochemical, and virologic evidence of chronic liver disease.
- Current substance use or participation in opioid substitution program should **not** exclude patients from HCV treatment evaluation.

History	<ul style="list-style-type: none"> • Date of hepatitis C diagnosis • Risk factors for HCV acquisition: MSM, IVDU, etc. • Alcohol use history: past and current (AUDIT-C) • IVDU history: past and current • Presence of viral hepatitis coinfections: hepatitis A and hepatitis B • Prior staging of liver fibrosis • Prior treatment for hepatitis C • Complications of liver disease: ascites, GI bleeding, jaundice, encephalopathy • Extrahepatic manifestations of HCV: cryoglobulinemia, arthralgia, porphyria cutanea tarda • Current medications (including over-the-counter) and herbal supplements
Physical Examination	Perform a thorough physical examination with special attention to the abdomen, skin, and neurologic system. Note that many patients may display no abnormalities. Abnormal findings suggestive of liver disease include: jaundice, spider angiomas, palmar erythema, caput medusa, splenomegaly, and gynecomastia.

Imaging	<ul style="list-style-type: none"> • Baseline imaging- ultrasound to assess for portal hypertension, splenomegaly. • CT scan with contrast or MRI if HCC is suspected (particularly in patients with advanced fibrosis).
Initial Work-up	<ul style="list-style-type: none"> • General: CMP, CBC, TSH. • HIV-specific: CD4, HIV VL. • Disease specific: HCV viral load, HCV genotype, Alpha-fetoprotein, PT. • Chronic viral hepatitis serology: Hepatitis B surface Ag, core Ab IgG (if any positive, send HBV PCR VL), surface Ab titer, Hepatitis A IgG Ab.
Staging	<ul style="list-style-type: none"> • History and results of liver biopsy (note that liver biopsies are very rarely required for staging given the noninvasive options below). • Noninvasive markers for assessing fibrosis: Calculate Fib-4, https://www.hiv.uw.edu/page/clinical-calculators/apri • Calculate APRI (AST to Platelet Ratio Index), https://www.hepatitisc.uw.edu/page/clinical-calculators/apri • FibroSure®, FibroTest®, and FIBROspect® are proprietary markers that can be ordered • Noninvasive imaging: <ul style="list-style-type: none"> • Vibration-controlled transient elastography (FibroScan®) • Acoustic radiation force impulse (ARFI) imaging • Two-dimensional shear wave elastography (Aixplorer®) • Magnetic resonance elastography (MRE)
Assess for Comorbidities	<ul style="list-style-type: none"> • Diabetes mellitus, metabolic syndrome • Cardiac, pulmonary, neurologic comorbidities • Additional liver comorbidities: alcoholic liver disease, NASH (ultrasound, history of metabolic syndrome), hemochromatosis (iron studies), autoimmune liver disease (ANA)
Preventative	<ul style="list-style-type: none"> • Vaccinate for hepatitis A, B if not immune. • Vaccinate against <i>Streptococcus pneumoniae</i> and influenza as per ACIP guidelines.
Counseling	<ul style="list-style-type: none"> • On prevention of transmission and natural history of HCV infection • On alcohol use: 50 g/day or more of alcohol leads to ongoing hepatotoxicity and accelerated progression of liver fibrosis • On use of common over the counter drugs that are hepatotoxic such as acetaminophen • Ongoing IVDU: refer to mental health provider and/or substance use program



- HIV/HCV-co-infected persons should be treated and retreated in the same manner as persons without HIV infection, after recognizing and managing interactions with antiretroviral medications, <https://www.hepatitis.va.gov/provider/guidelines/hcv-treatment-considerations.asp>. Initial treatment of HCV Infection and retreatment of persons in whom prior therapy has failed are found on VA website. “Summary Table: Treatment Considerations and Choice of Regimen for HCV-Monoinfected and HIV/HCV-Coinfected Patients”, <https://www.hepatitis.va.gov/provider/guidelines/hcv-treatment-considerations.asp>. Drug-drug interactions (DDIs) with HIV ARV therapy should be taken into account when selecting a hepatitis C regimen, <http://www.hep-druginteractions.org>.
- Antiretroviral therapy may slow liver disease progression in HIV/HCV co-infected patients and should therefore be considered for all co-infected patients regardless of CD4 cell count.
- Sofosbuvir (SOF)-containing regimens should not be used in patients with severe renal impairment (eGFR <30 mL/min) or end-stage renal disease requiring dialysis.
- Anyone considering treatment with DAA should be screened for HBV, and those with active HBV should receive hepatitis B antiviral therapy.
- The landscape of DAA treatment is continuously evolving. Materials from VA Center of Excellence are available at <https://www.hepatitis.va.gov/products/index.asp>. The most current national guidelines are available at <https://hcvguidelines.org>.
- The current DAAs available on the market include: sofosbuvir, simeprevir, daclatasvir, ledipasvir-sofosbuvir, paritaprevir/ritonavir/ombitasvir/dasabuvir, elbasvir/grazoprevir, velpatasvir/sofosbuvir; (sofosbuvir/velpatasvir/voxilaprevir and glecaprevir/pibrentasvir were recently approved). See **HCV Direct-Acting Antiviral Agents by Drug Class, Table 4** in PDF <https://www.hepatitis.va.gov/provider/guidelines/hcv-treatment-considerations.asp> or <https://www.hepatitis.va.gov/provider/guidelines/HCV-DAA-Class.asp>



WHEN TO REFER

- Consultation with a provider with expertise in HIV and HCV care is advised before initiating HCV treatment in an HIV/HCV-co-infected patient.
- When patient has advanced fibrosis or cirrhosis, referral to hepatology for entry into care is indicated, along with screening for HCC and esophageal varices.

! POTENTIAL ARV INTERACTION

Treatment of HIV/HCV-co-infected patients requires continued awareness and attention to the complex drug interactions that can occur between DAAs and antiretroviral medications.

Changes in ARV therapy can be made by an experienced provider in treatment of co-infected HIV-hepatitis C only if deemed necessary. Multiple sources to assess the interactions are available at <https://www.hepatitis.va.gov> for updates.

! POST CURE, THE RISK OF REINFECTION AND HCC PERSISTS

- Cure is defined by a sustained virological response (SVR) 12 (absence of virus in the blood 12 weeks after the end of therapy).
- Post cure, HCV Ab will remain positive but HCV PCR will be negative unless there is reinfection.
- There is risk of reinfection in patients with high risk behaviors (IVDU, unprotected sex), hence screening with HCV PCR should be performed annually in patients with HIV who were treated but have ongoing risk.
- For patients with advanced fibrosis, screening for HCC should continue to occur post-cure with a liver ultrasound every six months.

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HIV and Aging

KEY POINTS

- Almost half of patients with HIV infection in the USA are now aged 50 years and older.
- Due to the immune activation of HIV and its co-infections, patients with HIV are more likely to have immunosenescence, as in the elderly, resulting in organ dysfunction and increased susceptibility to infection and malignancy. Even in controlled HIV infection, patients experience excess morbidity and mortality.
- The common conditions of aging, such as neurocognitive decline, cardiovascular disease, malignancy, osteoporosis, metabolic syndrome, and frailty, disproportionately affect the HIV population.
- To counter the effects of aging in the HIV population requires a healthy lifestyle, immunizations, strict virologic control, consideration of polypharmacy, and attention to preventive medical services, such as cancer, renal function, and lipid screenings.



BACKGROUND

- In 2014, about 45% of Americans with HIV infection were aged 50 and older, 27% were 55 and older, and 6% were 65 and older.
- The increase in older patients with HIV arises from two sources. First, patients infected with HIV are living longer due to antiretroviral (ARV) therapy. The second source is the acquisition of new HIV infection.
- People aged 50 and over accounted for 17% of the new 39,513 HIV diagnoses in the USA in 2015. In this age group, 49% of new diagnoses were among gay and bisexual men, 15% were among heterosexual men, 23% were among heterosexual women, and 12% were injection drug users.
- In 2014, 40% of people aged 55 and older had AIDS at the time of HIV diagnosis. Late diagnoses occur because health care providers may neglect to test older patients for HIV infection. Also, older patients may not consider themselves to be at risk of HIV infection or may mistake HIV symptoms for those of normal aging.
- Dating is increasingly common among widowed and divorced people, in part due to social media. They may be less aware of their risks for HIV infection compared to younger patients and may be less likely to protect themselves.
- In an era of drugs for erectile dysfunction, older men may be more sexually active, and thus may have the **same HIV risk factors as younger persons**, including ignorance about HIV prevention and having multiple sex partners.

Note: Some medications mentioned in this chapter may not be available on the VHA National Formulary (<https://www.pbm.va.gov/NationalFormulary.asp>). Consult VA pharmacists for alternatives.

- Post-menopausal women, without the concern for pregnancy, may be less likely to have their partners use condoms. Age-related vaginal atrophy may also increase their susceptibility to HIV infection.
- Older people may be less likely to discuss their sexual behavior or drug use with their healthcare providers; who, in turn, are less likely to ask older patients about these issues.
- HIV infection creates a condition of premature physiologic and immunologic aging that predisposes individuals to earlier onset of the usual comorbidities of aging. Due to ARV therapy, the life expectancy of newly diagnosed asymptomatic patients with HIV infection now approaches that of patients who are uninfected. Thus, there is concern that as our HIV population ages, the conditions of aging will severely impact the quality of life of these patients.
- Older patients who are HIV-infected are more adherent to ARV therapy. In one meta-analysis, older age reduced the risk of non-adherence by 27%.

Immunologic Effects of Aging and HIV

Inflammaging is a term coined to describe the systemic low-grade inflammation that occurs in age- and HIV-mediated immunosenescence that may contribute to the development of cardiovascular disease, cancer, metabolic syndrome, type 2 diabetes, obesity, neurodegeneration, arthritis, osteoporosis, depression, and frailty. These conditions have been termed HIV-associated non-AIDS (HANA) comorbidities. In the Veterans Administration Cohort Study (VACS), the prevalence of HANA conditions was 60–63% [20]. Other studies have reported a HANA prevalence of 94%, with patients who are HIV-infected over age 50 in the USA having an average of three comorbid conditions. Multi-morbidity (two or more comorbidities) developed 10 years earlier in HIV patients compared with patients who are uninfected.

Even in aviremic patients with HIV, there is excessive inflammation, due to loss of regulatory CD4 cells, thymic atrophy, co-infections, and loss of gut mucosal integrity with microbial translocation. Indicators of inflammaging include increased levels of activated CD4 and CD8 cells and of inflammatory cytokines, high CD8 counts, and activation of the coagulation pathway. Viral antigens and the inflammatory mediators they elicit promote CD8 proliferation and differentiation leading to their replicative senescence. These late-differentiated CD8 cells contribute to inflammaging. Increased levels of senescent CD8 cells are reflected in low CD4/CD8 ratios, which is associated with increased mortality in HIV patients. Lower CD4/CD8 ratios are associated with an increased risk of age-associated comorbidities both in HIV patients and the elderly. Due to the downregulation of interleukin-2 and the thymic involution of aging, older patients with HIV are less likely to have robust immune reconstitution when treated with ARV therapy.

A wealth of data on comorbidities in Veterans with HIV has been obtained by the VACS which is a prospective observational longitudinal cohort of HIV-infected and -uninfected Veterans matched for age, race/ethnicity, sex, and clinical site. VACS data has also been used to derive the VACS Index, a composite score of disease severity of persons with HIV infection which utilizes age, viral load, CD4 count, markers of renal and liver function (eGFR and FIB-4, respectively), anemia, and hepatitis C virus co-infection. A higher VACS Index score is associated with increased mortality in persons with HIV and multiple poor health outcomes (risk for hospitalizations, intensive care unit admissions, fragility fractures, neurocognitive impairment, cardiovascular events, frailty, and all cause mortality).

Neurocognitive Disorder

Neurocognitive impairment (NCI), or deficits in memory, language, visuospatial ability, and executive function that exceed age-related norms, is one of the more common and persistent complications associated with HIV, even in the era of effective treatments. HIV-Associated Neurocognitive Disorders (HAND) includes three entities, in order of increasing severity: asymptomatic neurocognitive impairment (ANI; mild cognitive impairment, no impact on daily function) and mild neurocognitive disorder (MND; mild cognitive impairment, modest impact on daily function) to HIV-associated dementia (HAD; marked impairment in cognition and daily function). About half of patients with HIV experience some degree of neurocognitive impairment, with attention, learning, memory, and executive functioning being the domains most commonly affected in the era of ARV therapy.

In the post-ARV therapy era, the prevalence of HAD has decreased (from 18% to <5%), with increased prevalence of mild symptomatic impairment (from 12% to 17%) and ANI (from 20% to 28%). Factors that may contribute to increased rates of ANI and MND include HIV-specific characteristics (e.g., infiltration of virus in CNS prior to ARV therapy initiation, lower CD4 nadir), effects of ARV therapy (e.g., inability to eradicate virus from CNS, potential neurotoxic effects of select agents), medical comorbidities (e.g., hepatitis C and associated liver disease, cardiovascular disease, metabolic syndrome) and mental health comorbidities (e.g., depression, substance abuse), individual differences (e.g., older age, low socioeconomic status, limited cognitive reserve), and health-related behaviors (e.g., reduced physical activity, poor nutritional status). Higher VACS Index scores are also associated with worse neurocognitive performance and an increased risk for developing neurocognitive impairment in HIV-infected persons with normal baseline neurocognitive function.

Malignancy

HIV infection increases the risk of infection-related cancers that are both AIDS-defining, such as Kaposi sarcoma, cervical cancer, and non-Hodgkin lymphoma, and non-AIDS-defining cancers, such as rectal and liver cancers. Certain infec-

tion-unrelated cancers are also increased in patients with HIV, including Hodgkin lymphoma, melanoma, and lung cancer.

The risk of Kaposi sarcoma is increased about 500 times in patients infected with HIV and they are 12 times more likely to be diagnosed with non-Hodgkin lymphoma. Women with HIV infection are 3 times more likely to be diagnosed with cervical cancer than non-HIV-infected women. There is a 26% increase (50% for light-skinned people) in the relative risk of melanoma in HIV patients. The incidence of lung cancer is estimated to be increased about 2 to 4 times in patients living with HIV.

However, prostate and breast cancer, two of the most common age-associated malignancies, are not increased in HIV patients. The factors responsible for higher rates of select cancers are both physiologic and behavioral. Immunosuppression and chronic inflammation increase the likelihood of cancer. Substance abuse and sexual behaviors increase the risk of exposure to carcinogenic agents (tobacco, alcohol) and oncogenic viruses (HHV-8, human papilloma virus, and hepatitis B and C viruses).

In the Strategic Timing of Antiretroviral Treatment (START) trial, a low CD4 cell count increased the risk for melanoma and lung and liver cancers, and ARV therapy decreased the risk of AIDS-defining cancers and infection-related cancers. ARV therapy was also associated with a nonsignificant decrease in non-infection-related cancers. In one study, the lower risk of infection-unrelated cancers in the immediate-ARV therapy group did not reach statistical significance. There are conflicting data regarding whether cancers present at younger ages in patients with HIV. In one study, patients with HIV had earlier age of onset for myeloma, lung cancer, and anal cancer by 3 to 4 years, as compared to patients who are non-infected. However, in the VACS cohort, there were no differences in the age at presentation of non-AIDS-defining cancers.

Cardiovascular Disease

Cardiovascular disease is another common age-related morbidity in the general population that is also more prevalent in the HIV population. HIV patients in the USA treated with ARV therapy have twice the risk for myocardial infarction (MI), sudden cardiac death, and heart failure compared to the general population. The factors responsible for this increased risk include: higher rates of traditional risk factors (smoking, hypertension, diabetes); increased levels of inflammation and T-cell senescence; cardiac toxicities of specific ARV therapy agents; and HIV-specific factors. Increased levels of monocyte activation, endothelial dysfunction, and T-cell senescence in HIV patients are associated with atherosclerosis. HIV-specific factors associated with MI risk are longer durations of ARV therapy use, lower nadir CD4 cell counts, lower CD4 cell counts, and higher viral loads. Although Veterans who are HIV-infected have a higher incidence of MI than Veterans who are non-infected (2.02 vs. 1.28 per 1000 person years), the average age at initial MI diagnosis did not differ between the two groups in the VACS. HIV infection is also associated with a 19% increased risk of peripheral vascular

disease. For HIV patients with sustained CD4 counts <200 cells/mm³ the risk of incident peripheral vascular events is almost two-fold higher. However, for those with sustained CD4 counts ≥ 500 cells/mm³ there is no excess risk.

Liver Disease

Compared with patients who are HIV-negative, patients with HIV with HBV or HCV co-infection are more likely to suffer hepatic steatosis and fibrosis and have rapid progression to cirrhosis with decompensation. Hepatic steatosis is associated with metabolic syndrome and is more common in HIV patients than in the general population. Older age at the time of HCV acquisition and alcohol consumption are strong predictors of liver fibrosis regardless of HIV status; in patients who are HIV-infected, lower CD4 counts are associated with hepatic fibrosis. Successful treatment of hepatitis C decreases incidence of hepatocellular carcinoma, hepatic decompensation, cardiovascular events, and bacterial infections; it decreases overall mortality from liver-related and non-liver-related causes.

Metabolic Syndrome

The metabolic syndrome, which includes obesity, dyslipidemia, hyperglycemia, and hypertension, is a clustering of risk factors for cardiovascular disease. In HIV patients, the most common features of metabolic syndrome are hypertension, low HDL levels, and hypertriglyceridemia. The latter two factors, low nadir CD4 counts, and longer duration of HIV infection all contribute to the development of diabetes. Treatment with protease inhibitors and stavudine also increases the risk of insulin resistance.

Obesity and sedentary lifestyle are the major contributors to the development of metabolic syndrome. However, patients who are HIV-infected with metabolic syndrome were more likely to have a lower BMI and a smaller waist circumference than patients who are not HIV-infected. Metabolic syndrome is also affected by fat distribution and adipocyte function. HIV patients, especially those treated with thymidine analogs (zidovudine, stavudine), are more likely to have lipodystrophy, which is associated with insulin resistance and dyslipidemia. Patients who are HIV-infected often have increased visceral fat despite lower waist circumference than their counterparts who are not infected.

The prevalence of metabolic syndrome increases with aging. In the Data-Collection on Adverse Effects of Antiretroviral Drugs (D:A:D) study, which follows $>33,000$ individuals with HIV over time, there is an increasing prevalence of metabolic syndrome, from 19.4% in 2000–2001 to 41.6% in 2006–2007, in part due to aging of the cohort. A common comorbidity with metabolic syndrome is obstructive sleep apnea (OSA). Although OSA is about half as common in patients with HIV as in the general population, patients with HIV with OSA are younger, less likely to have hypertension, and have lower body mass indexes.

Osteoporosis/Osteopenia

Fracture rates are higher in the HIV population and increase with advancing age. In the Multicenter AIDS Cohort Study (MACS), the fracture rate of men who are HIV-positive aged 50–59 years was double that of men who are HIV-negative in the same age group. The high rate of osteoporosis in the HIV population is driven by both traditional risk factors, such as female sex, corticosteroid use, smoking, and low body mass index, as well as HIV-specific factors, such as receiving ARV therapy in general, specific ARV therapy agents (tenofovir disoproxil fumarate), hepatitis C co-infection, cumulative viremia, and low CD4 count at ARV therapy initiation. In the VACS, unadjusted risk for fragility fracture was 32% higher for men with HIV. After adjusting for demographics, comorbidities, smoking, and alcohol use, HIV infection remained associated with fracture risk [hazard ratio: 1.24]. However, adjusting for BMI reduced this association. Current protease inhibitor use was also associated with fragility fractures [hazard ratio 1.41].

Renal Disease

The management of renal disease in aging patients who are HIV-infected is increasingly important. Factors associated with an increased risk of chronic kidney disease in the HIV population include older age, female sex, diabetes, hypertension, injection drug use, lower CD4 cell count, specific antiretroviral drugs (tenofovir disoproxil fumarate), history of acute kidney injury, hepatitis C co-infection, and higher HIV viral loads. In the VACS cohort, the incidence of end-stage renal disease in HIV-infected Veterans was significantly higher (2.56 vs. 1.68 per 1000 person-years), and the age at presentation was younger than in Veterans who are not HIV-infected (56.0 vs. 59.4 years).

Frailty

Frailty is defined as a state of increased vulnerability that occurs with aging. The frailty phenotype (FP) includes three or more of the following: weakness (assessed by grip strength), low physical activity, slowed motor performance (measured by walking speed), exhaustion, and unintentional weight loss. In regard to weakness, a higher VACS Index score is associated with decreased strength measures. The presence of the FP predicts acute illness, falls, cognitive decline, hospitalization, disability, dependency, and mortality. The prevalence of frailty in the USA is 7–12% among community-living persons aged 65 years and older.

In the MACS, men with HIV were 38% more likely than HIV-negative men to present with frailty during a clinic visit. In the HIV-positive group, those with frailty, as compared to those not classified as frail, were twice as likely to have a history of AIDS, had lower CD4 counts, and were more likely to have a detectable viral load. The likelihood of transitioning from the non-frail to the frail group increased with older age, black race, smoking, HCV infection, depressive symptoms, history of diabetes, and kidney disease. Other cohort studies have found

that many patients with HIV manifest with frailty even in middle age. In the VACS, chronic obstructive pulmonary disease was associated with prefrailty and frailty in Veterans who were HIV-infected and uninfected.

Chronic inflammation is a contributing factor to frailty in older adults and patients with HIV. The mechanisms of how immune activation is linked to frailty are unclear. Chronic cytomegalovirus (CMV) infection may activate immune and inflammatory pathways that promote the frailty and other HANA conditions. The VACS Index provides a method to estimate the level of physiologic frailty.

Management of the Aging Patient with HIV Infection

A cornerstone of the management of the older patients with HIV is to focus on mitigating modifiable risk factors for major chronic illnesses. This includes smoking cessation and managing alcohol and substance abuse. Stimulant use in particular is associated with renal disease and increased mortality.

To lessen the risk or impact of neurocognitive impairment, it is critical to address the spectrum of aforementioned contributory factors. Initiation of ARV therapy as soon as possible after HIV diagnosis is strongly recommended. Aggressive management of vascular risk factors (hypertension, diabetes, smoking, and obesity) is critical as these appear to play a leading role in HAND and contribute to other conditions that negatively affect cognition (e.g., vascular brain injury). Thus, many factors could contribute to the onset, maintenance, or progression of HAND. The period between the onset of vascular risk factors and emergence of neurocognitive impairment (NCI) varies, so risk factors should be addressed long before neurocognitive impairment is apparent. Similarly, early and ongoing intervention for mental health conditions (e.g., depression, substance dependence) is vital. Encouraging activities that stimulate cognition, including hobbies, social engagement, physical activity, and employment, promotes enhanced cognitive reserve. Early initiation of these activities is beneficial. For individuals with NCI, individual or group cognitive rehabilitation may help to lessen the impact of cognitive difficulties in daily life. Cardiovascular risk assessment using the currently available prediction models underestimates risk in the HIV population, but nevertheless may help guide the need for lifestyle and pharmacologic interventions.

To optimize hepatic health, treatment of hepatitis B or C, as necessary, and protection against hepatitis A and B with immunization, is recommended. To prevent nonalcoholic fatty liver disease, obesity and dyslipidemia must be controlled. To minimize the deterioration of renal function with age requires the appropriate selection of ARV therapy agents, reduction of the use of other potential nephrotoxic medications, treatment of hepatitis C, and the control of diabetes, substance abuse, and hypertension. Patients with HIV who evidence pre-end stage renal disease should be treated with statins and aspirin to decrease the risk of cardiovascular disease.

To reduce cancer mortality for patients with HIV, clinicians should focus on reducing cancer incidence by promoting smoking cessation, moderation in alco-

hol consumption, adherence to ARV therapy, and treating HBV and HCV infections. Age-appropriate cancer screening should be performed, with particular focus on cervical, anal, and lung cancer due to the higher rates of these cancers in patients with HIV infection. Women who are HIV-infected should undergo a cervical PAP smear upon entry into care, with a repeat test at 6 months, and annually thereafter if the prior results were normal. Women with abnormal PAP results (atypical squamous or glandular cells, any grade of squamous intraepithelial lesion, or carcinoma) require colposcopy with biopsy. Anal PAP smears should be considered in men who have sex with men, women with a history of receptive anal intercourse or abnormal cervical PAP, and all patients with HIV with genital warts. Abnormal cytologic results should be followed by anoscopy and biopsy.

For lung cancer, an annual screening with low-dose computed tomography is recommended for those 55 to 80 years old with a 30 pack-year smoking history and current smoking or those that have quit within the past 15 years. Based on a lack of increased risk in the HIV population, breast, prostate, and colorectal cancer screening should follow the guidelines for the general population.

Encouraging physical activity and weight management will decrease the risk of metabolic syndrome, osteoporosis, cardiovascular disease, and age-associated functional decline. Applying principles of geriatric medicine, such as polypharmacy management, neurocognitive and functional assessments, fall prevention, and addressing end-of-life issues, will also improve the care of the aging HIV population.



WHEN TO REFER

- for neurocognitive decline, perform initial neurologic and psychiatric assessment, refer for formal neurocognitive testing, and obtain neuroimaging based on these assessments. Refer to individual or group cognitive rehabilitation for treatment for substance abuse, intervention as needed; formal smoking cessation program, as needed;
- for hepatitis C treatment, if not done in the primary HIV clinic;
- to endocrinologists for osteoporosis and difficult to control diabetes; or
- to a nephrologist when there is: a significant decline in GFR (i.e., by >25% from baseline or to <60 mL/minute/1.73 m²) that fails to resolve after nephrotoxic drugs are discontinued; albuminuria >300 mg/day; hematuria with either proteinuria or increasing blood pressure; or for advanced chronic kidney management (GFR <30 mL/minute/1.73 m²).



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KEY POINTS

- Hypertension is an independent, reversible risk factor for cardiovascular, cerebrovascular, and renal disease that is under diagnosed and undertreated.
- HIV-infected patients have a high prevalence of hypertension and other cardiovascular risk factors.
- In most cases, the treatment of hypertension should start with lifestyle modification. Other antihypertensive drugs may be useful, depending on the patient's additional comorbidities.

Note: This chapter does not address hypertensive emergency or urgency in detail.



BACKGROUND

Rationale for Detecting and Treating High Blood Pressure

- Elevated blood pressure (BP) is an independent risk factor for myocardial infarction (MI), stroke, heart failure, atrial fibrillation and kidney disease.
- The relationship between BP and these disease events is continuous; the risk of cardiovascular disease doubles for every 20 mm Hg increase in systolic BP or 10 mm Hg increase in diastolic BP. This effect applies across the spectrum of BP, from normal to severely elevated.
- The etiology of hypertension is multifactorial; monogenetic forms are rare. Key elements in the etiology are activation of neurohormonal systems; increased oxidative stress; altered cellular ion transport of sodium, potassium and calcium; and abnormalities of endothelial function and vascular reactivity, large artery compliance, and small artery/arteriolar resistance.
- In clinical trials, treatment of hypertension is associated with substantial reductions in the incidence of MI, stroke, and heart failure.
- “Prehypertension” (as defined in the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure [JNC 7], see **Table I** below) confers an increased risk of developing hypertension and often warrants therapeutic intervention. Because the short-term pharmaceutical treatment of prehypertension has not been shown to forestall the development of hypertension, some experts have questioned the benefit of labeling patients with this diagnosis.

Note: Some medications mentioned in this chapter may not be available on the VHA National Formulary (<https://www.pbm.va.gov/NationalFormulary.asp>). Consult VA pharmacists for alternatives.

- Although hypertension can be controlled for most patients by a combination of lifestyle changes and pharmaceutical therapy, hypertension remains poorly controlled for many patients.

Special Considerations regarding Hypertension, ARV Therapy, and CD4 counts

Although a relationship between certain specific antiretroviral agents and other components of the metabolic syndrome, such as hyperlipidemia and elevated blood glucose, has been established, it is not clear whether HIV or specific ARVs are independent risk factors for hypertension.

Some early studies suggested a link between PI-based ARV therapy and elevated BP. Larger studies were later conducted, including the D:A:D study, and found that this relationship was accounted for by other factors, such as age, race, and, in particular, increases in BMI that occurred after initiation of ARVs. Another study suggests a link between the duration of ARV therapy and BP. Prolonged ARV therapy, defined as 2-5 years in duration, was independently associated with development of hypertension in the MACS study, whereas ARV therapy of <2 years in duration was not.

In one study, integrase inhibitor use was associated with lower systolic blood pressure, whereas stavudine exposure was associated with hypertension.

The degree of immunosuppression may also affect hypertension. Patients with HIV who maintain a CD4 cell count above 500 cells/μL have a lower risk for a subsequent diagnosis of hypertension. Conversely, nadir CD4 counts below 200 cells/μL are a risk factor for hypertension.

Treatment Goals (See Table I)

- There is currently no firm consensus on optimal blood pressure targets between the major practice guidelines, although the targets are generally to achieve a BP below 140/90 with consideration of more aggressive lowering in those with diabetes or chronic kidney disease (CKD). Numerous factors including age, comorbidities, and medication tolerance should affect how the clinician approaches each individual patient. Listed below are the recommendations from a few of the guidelines:
 - Current VA/DoD recommendations (which as of this publication are dated 2014)
 - Adult patients <140/90
 - Diabetics <140/85
 - CKD <140/90
 - American Heart Association (AHA)
 - Most adult patients <140/90 (can consider lower if diabetic or with CKD)

- Adult patients >80 years old <150/90
- Kidney Disease Improving Global Outcomes (KDIGO) and American Diabetes Association (ADA)
 - Adult patients with CKD but **without albuminuria or diabetes** <140/90
 - Adult patients with diabetes but **without albuminuria** <140/90
 - Adult patients with diabetes **and** CKD <130/80
- The JNC 8 report was narrower in scope than the previous JNC 7 report, and therefore recommendations from both publications are included here for reference.
 - JNC 7
 - Adult patients <140/90
 - Diabetics and/or CKD <130/80
 - JNC 8
 - Adults <60 years old <140/90
 - Adults **with diabetes or CKD** <140/90
 - Adults >60 years old **without diabetes or CKD** <150/90
- The guidelines acknowledge that these cutoffs are maximum thresholds and that patients already tolerating pressures lower than these goals should not have their medications adjusted to allow BP to increase.
- Target blood pressure recommendations will likely continue to be an area of intense debate and research in the coming years. The 2002 Prospective Studies Collaboration demonstrated reduced ischemic heart disease mortality with lower BP to a threshold of 115/75. More recently, the SPRINT trial showed significant decreases in fatal and non-fatal cardiovascular outcomes as well as all cause mortality in patients >50 years of age with high cardiovascular risk but without diabetes treated to <120 systolic as compared to <140 systolic.



SCREENING

- The 2015 United States Preventative Services Task Force (USPSTF) guidelines recommend screening all patients over the age of 18.
- Although an optimal screening interval has not been defined, the current VA/DoD guidelines recommend annual BP screening. JNC 7 recommends screening for hypertension every two years for patients with BP <130/85, and more frequently for patients with BP >130/85.
- Checking BP at all clinic visits is encouraged.

How to Measure Blood Pressure in the Office

- The patient should be seated in a chair for five minutes, feet on the floor, with arm at heart level.
- The patient should not have smoked, had caffeine, or exercised within 30 minutes before BP measurement.
- Cuff bladder should encircle $\geq 80\%$ of arm.
- The average of at least two measurements per office visit should be recorded.
- The diagnosis of prehypertension or hypertension (See **Table 1**) is based on the presence of an elevated BP taken on at least two office visits over a two-month period. For Stage 2 hypertension, evaluation or referral should be performed within one month of the initial measurement.
- Home blood pressure readings can be of value in determining if the patient has elevated BPs only in the doctor's office (white coat hypertension) and in some cases may reveal higher BPs than what are obtained in the clinic (masked hypertension). If home and office readings are inconsistent, the patient can be instructed to bring their home blood pressure cuff to the office. The clinician can then observe how the patient is measuring their BP and can directly compare the measurements to those obtained in the clinic for concordance.
- Another alternative to confirm suspected hypertension (HTN) is to order an ambulatory blood pressure monitor (ABPM). This test requires the patient wear a BP cuff attached to a programmable recorder for 24 hours with BP measurements automatically obtained in pre-specified intervals, typically 20-30 minutes, throughout the day and night. The USPSTF guidelines highly recommend ABPM for confirming the diagnosis of HTN.

Table 1. Definition and Treatment of High Blood Pressure

Blood Pressure (mmHg)	Classification	Treatment (associated tables in bold)
<120/80	Normal	No treatment indicated. Encourage lifestyle measures as shown in Table 3 .
Systolic: 120-139 or Diastolic: 80-89	Prehypertension	Lifestyle modification (Table 3) and Treat comorbidity,* if present and appropriate. (consider goal <130/80 if diabetic with CKD and albuminuria)#
Systolic: 140-159 or Diastolic: 90-99	Stage I hypertension	Goal: BP <140/90 (consider goal <130/80 if diabetic and/or with CKD and albuminuria)# Lifestyle modification (Table 3) and Start medication • If no comorbidity,* use thiazide (preferred) or

Blood Pressure (mmHg)	Classification	Treatment (associated tables in bold)
-	-	angiotensin-converting enzyme inhibitor (ACEI), angiotensin receptor blocker (ARB), calcium channel blocker (CCB), or fixed-dose combination (FDC) of agents. <ul style="list-style-type: none"> If comorbidity,* choose from table of disease-specific anti-hypertensives (Table 4).
Systolic: >159 or Diastolic: >99	Stage 2 hypertension	Goal: BP <140/90 (consider goal <130/80 if diabetic and/or with CKD and albuminuria)# Lifestyle modification (Table 3) and Start 2 medications <ul style="list-style-type: none"> If no comorbidity,* use thiazide plus ACEI/ARB, or CCB, dosed separately or as an FDC. If comorbidity,* choose from table of disease-specific anti-hypertensives (Table 4). Consider gradual BP reduction starting with 1 agent for patients at risk of postural hypotension (e.g., elderly).
<p>* Comorbidities include diabetes, CAD, peripheral vascular disease, cerebrovascular disease, heart failure, or renal disease defined as a reduced GFR (CrCl <60 mL/min/1.75 m²) or albuminuria (>300 mg/dL).</p> <p># The JNC 7 Report, the KDIGO 2012 Management of Blood Pressure Guidelines, and the ADA Standards of Medical Care in Diabetes 2016 include recommendations for a target BP of <130/80 for patients with diabetes and CKD with albuminuria. AHA 2015 Scientific Statement on Treatment of Hypertension in Patients with Coronary Artery Disease also recommend a target BP of <130/80 for patients with known CAD, previous MI, stroke or transient ischemic attack, or CAD equivalents (carotid or peripheral arterial disease, abdominal aortic aneurysm).</p>		

Adapted from VA/DoD Guidelines, JNC 7 Report, and AHA Guidelines. See **References**, VA/DoD, Chobanian, Rosendorff.

Office Evaluation of the Hypertensive Patient

Specific findings of end-organ damage or cardiovascular comorbidities should guide the choice or intensity of therapy and prompt possible additional workup. The basic evaluation of the hypertensive patient, adapted from the JNC 7, is shown in **Table 2**. Although <5% of patients have secondary hypertension, clinicians should be alert to possible underlying causes such as Cushing syndrome or sleep apnea. Workup of secondary hypertension is addressed in VA/DoD guidelines at <http://www.healthquality.va.gov/>.

Table 2. Evaluation of Hypertensive Patients for End-Organ Damage and Treatable Comorbidities

Component	Evaluation	Possible Findings
History	<ul style="list-style-type: none"> • Review of systems • Past medical history • Health-related behavior • Family history 	<ul style="list-style-type: none"> • Dyspnea, chest pain, edema, polyuria/polydipsia • CAD, CHF, diabetes, renal disease • Tobacco use, physical activity • Early CAD, diabetes
Physical Examination	<ul style="list-style-type: none"> • Vital signs • Ophthalmologic examination • Peripheral circulation • Cardiac examination • Respiratory examination 	<ul style="list-style-type: none"> • Elevated BMI • Arteriovenous nicking, papilledema (hypertensive retinopathy) • Diabetic retinopathy • Bruits: carotid, abdominal, or femoral (peripheral vascular disease) • Decreased peripheral pulses • LVH, S3, S4, distended neck veins (hypertrophy, failure) • Crackles/wheezes
Studies	<ul style="list-style-type: none"> • Electrolytes, BUN, Cr, glucose, Ca²⁺ • Fasting lipids • Urinalysis • ECG • Spot urine protein/Cr ratio 	<ul style="list-style-type: none"> • Decreased renal function, diabetes, hyperaldosteronism • Hyperlipidemia • Proteinuria, glycosuria, hematuria • LVH, CAD

Rx MANAGEMENT

Initial Management

Lifestyle modification

- **All hypertensive patients should be encouraged to attempt lifestyle modification. See Table 3.**
- **Whenever possible, tobacco use should be addressed. See Tobacco Use, p. 127.**

Table 3. Lifestyle Modifications Shown to Reduce Blood Pressure

Area to Modify	Goals	Anticipated SBP Reduction
Diet	DASH (Dietary Approaches to Stop Hypertension) diet: <ul style="list-style-type: none"> • HIGH in fruit/vegetables, lean protein, low-fat dairy products, nuts, fiber, K⁺, Mg⁺⁺, Ca⁺⁺, whole grains (risk of hyperkalemia in patients with renal disease) • LOW in lean red meat, sugars For specific dietary recommendations, including serving sizes and ingredients, see the DHHS online DASH diet guide, https://www.nhlbi.nih.gov/ . Low sodium diet: ≤2.4 g/day	8-14 mm Hg
Exercise	>30 minutes of aerobic exercise per day, most days of the week <ul style="list-style-type: none"> • Aerobic activity = brisk walking 	4-9 mm Hg
Alcohol	≤2 alcoholic drinks/day (men) or ≤1 drink/day (women) <ul style="list-style-type: none"> • 1 drink = 0.4 oz (12 g) of ethanol: 12 oz beer, 5 oz wine, or 1.5 oz 80-proof (40%) liquor See Alcohol Use , p. 91.	2-4 mm Hg
Weight	Maintain BMI 18.5-24.9 <ul style="list-style-type: none"> • BMI = weight (kg)/height (m²) • U.S. DHHS BMI calculator, http://www.nhlbi.nih.gov/ 	5-20 mm Hg per 10 kg weight loss
<p style="text-align: center;">Resources</p> <p>Diet: The Healthier US Veterans program has useful dietary and nutritional information at http://www.hiv.va.gov/.</p> <p>Exercise and weight loss: The VHA MOVE program is a national weight management program for veterans; for further details, see http://www.move.va.gov.</p> <p>Alcohol misuse: See Alcohol Use, p. 91. Also, VA resources for patients on alcohol and drug use are available at http://www.hiv.va.gov/.</p>		

Adapted from JNC 7 Report. See **References**, Chobanian.

Medications

- **Many patients will require pharmacologic therapy.**
- **Considerations in choosing antihypertensive medication:**

- ACEIs, ARBs, BBs, and long-acting CCBs have been shown to reduce the cardiovascular complications of hypertension.
- The Eighth Report of the Joint National Committee (JNC 8) favors thiazide and CCBs over ACEI/ARB in the black patient population.
- In the absence of known coronary disease or congestive heart failure, BBs are not recommended for first-line treatment of HTN, given their association with insulin intolerance and increased risk of stroke, particularly among smokers.
- Many patients require 2 agents for sufficient control. Add a second agent if upward titration of the initial agent does not adequately control BP.
- Patients with Stage 2 hypertension generally should be started on 2 drugs. One study has shown the combination of an ACEI + a dihydropyridine CCB to be associated with decreased mortality and cardiovascular events compared with an ACEI + a thiazide; however, many experts include a thiazide in first-line therapy.
- Patients with renal or cardiovascular comorbidities may gain particular benefit from specific types of antihypertensive drugs (See **Table 4** and **Table 5**).
- Many antihypertensive drugs that are commonly prescribed together are marketed as single-tablet FDCs. These can be useful if the patient tolerates the same dosage of each drug given separately.
- Whenever possible, use medications that can be given once daily to promote adherence.

Table 4. Classes of Anti-hypertensives Favored in the Setting of Specific Comorbidities

Comorbidity	Diuretic	BB	ACEI	ARB	CCB	Aldosterone Antagonist
CHF	x	x	x	x	-	x
Post-MI	-	x	x	-	-	x
High Risk of CAD	x	x	x	-	x	-
Diabetes	x	o	x	x	x	-
CKD	-	-	x	x	-	-
Prevention of Recurrent Stroke	x	-	x	-	-	-

Adapted from JNC 7 Report. See **References**, Chobanian.

“O” Not recommended as monotherapy for HTN, and may worsen glucose homeostasis

Evaluation of Treatment Response

- Home BP monitoring can provide extremely useful information on BP control; BP cuffs for home use can be ordered through the VA Prosthetics Service. Devices with a memory function are preferable to patient recall or diary-keeping.
- Patients should be seen within one month of initiating therapy to assess efficacy, adherence, and toxicity. Patients requiring blood tests, those at high risk of end-organ damage, and those at risk of postural hypotension should be seen earlier.
- If BP is controlled to the target range, adequacy of control should be re-evaluated at least every 3-6 months.
- If BP is not controlled:
 - Explore adherence to regimen and educate patients about the importance of controlling hypertension.
 - Be alert to use of concomitant medications that may increase BP (e.g., NSAIDs, decongestants, erythropoietin, cyclosporine) and to substance use (e.g., alcohol, methamphetamine, cocaine).
 - Consider titration of initial drug regimen (usually doubling of dosage. See **Table 5**).
 - Add an agent from a second class. Agents shown to decrease morbidity and mortality are preferred (ACEI, ARB, BB, long-acting CCB, thiazide).
 - If a thiazide diuretic was not the initial drug chosen, it should be used as part of combination therapy unless contraindicated or not tolerated.
 - Consider joint care management with a clinical pharmacist.



WHEN TO REFER

Hypertension Clinic, Cardiology, or Renal

- Failure to achieve target BP after addition of second drug class
- Workup indicating secondary hypertension

Emergency Department

- Hypertensive emergency: BP > 180/120 complicated by:
 - Hypertensive encephalopathy
 - Intracranial hemorrhage
 - Acute MI or unstable angina
 - Dissecting aortic aneurysm
 - Acute heart failure with pulmonary edema

- Hypertensive urgency: BP >180/120 without target organ dysfunction. May see:
 - Headache
 - Epistaxis
 - Shortness of breath
 - Severe anxiety

Table 5. Anti-hypertensives: Drug Dosing and Interactions with ARVs

Notes

1. Dosages listed here are **for hypertension only**. Many of these agents (e.g., ACEIs) have additional indications, such as for congestive heart failure, for which lower dosages may be appropriate.
2. **“Divided”** means **“1/X of the daily dosage, given X times per day.”** Therefore, “100 mg daily, divided BID” means 50 mg BID. It does not mean 100 mg BID.
3. Drugs listed are representative of their respective classes only; other drugs within each class are also used, and specific dosing information should be followed.

Thiazide Diuretics

Pros: Chlorthalidone was shown to be cardioprotective in the ALLHAT study; thiazides are first-line therapy in JNC 7 and 8, VA/DoD guidelines. Thiazide diuretics and CCBs may be more effective than other antihypertensives and are first line in JNC 8 for African American patients.

Cons: Risk of hypokalemia and hypersensitivity phenomena. Monitor electrolytes periodically. Other potential adverse effects include rash, hyperglycemia, sexual dysfunction, and frequent urination. Should not be given to patients with a history of gout, as they may trigger attacks.

Generic Drug Name	Usual Starting Dosage/ Dosage Titration	Comments/Drug Interactions
Chlorthalidone	Start at 12.5-25 mg QD; may increase up to 50 mg QD; dosages >50 mg carry risk of hypokalemia without added benefit.	-

Generic Drug Name	Usual Starting Dosage/ Dosage Titration	Comments/Drug Interactions
Hydrochlorothiazide (HCTZ)	Start at 12.5-25 mg QD; may increase up to 50 mg QD (dosages >25 mg carry risk of hypokalemia with limited added benefit).	-

Beta-Blockers (BBs)

Pros: Useful for patients with concomitant CAD, CHF, previous MI, or those in need of rate control owing to atrial fibrillation or flutter.

Cons: May be associated with increased risk of stroke (particularly in smokers) and insulin resistance. When discontinuing, taper over course of 14 days to avoid rebound hypertension, angina, MI, or arrhythmia. May be less effective for patients without CAD, especially elderly patients. Use with caution in patients with reactive airway disease. Potential adverse effects include bradycardia, hypotension, fatigue, and sexual dysfunction.

Generic Drug Name	Usual Starting Dosage/ Dosage Titration	Comments/Drug Interactions
Atenolol	Start at 25-50 mg QD or divided BID; maximum 100 mg per day.	ATV and cobicistat and its combination drugs (Stribild, Genvoya, and Prezcofix) may ↑ atenolol concentrations; no dosage adjustment appears to be necessary.
Metoprolol tartrate	Start at 50 mg BID; maximum 225 mg BID.	CYP 2D6 substrate; PIs and cobicistat and its combination drugs (Stribild, Genvoya, and Prezcofix) may ↑ metoprolol levels.
Metoprolol Succinate (Extended Release)	Start at 50-100 mg QD; maximum 400 mg QD.	CYP 2D6 substrate; PIs and cobicistat and its combination drugs (Stribild, Genvoya, and Prezcofix) may ↑ metoprolol levels.
Propranolol	Start at 20 mg BID; maximum 640 mg per day in divided doses.	CYP 2D6 substrate; PIs and cobicistat and its combination drugs (Stribild, Genvoya, and Prezcofix) may ↑ propranolol levels.
Propranolol Extended Release	Start at 60 mg QD; maximum 640 mg QD.	Extended-release formulation cannot be substituted for immediate-release form on a mg per mg basis; may require dosage change.
Nebivolol	Start at 5 mg QD; maximum dose 40 mg QD.	CYP 2D6 substrate; PIs and cobicistat and its combination drugs (Stribild, Genvoya, and Prezcofix) may ↑ nebulolol levels.

Mixed Alpha-/Beta-Blockers

Pros: Useful for patients with known CAD or CHF.

Cons: Same as for beta-blockers. Avoid in patients with decompensated heart failure who are dependent on sympathetic stimulation. Alpha-Blockers are not recommended as first-line therapy because in one study initial treatment with an α -blocker resulted in worse cerebrovascular, heart failure, and combined cardiovascular outcomes than initial treatment with a diuretic.

Generic Drug Name	Usual Starting Dosage/ Dosage Titration	Comments/Drug Interactions
Carvedilol	Start at 6.25 mg BID; titrate slowly; usual dosage: 12.5-50 mg/day, divided BID.	CYP 2D6 substrate; PIs and cobicistat and its combination drugs (Stribild, Genvoya, and Prezcofix) may \uparrow carvedilol levels.
Labetalol	Usual dosage: 200-800 mg/day, divided BID.	IV form useful in hypertensive emergencies.

ACE Inhibitors

Pros: Cardioprotective, renal protective, first line therapy for non-black patients in JNC 8.

Cons: Avoid during pregnancy; use with caution in patients who are elderly, are fluid depleted, or have renal insufficiency. Risk of hyperkalemia, which may be higher in patients with advanced HIV disease or those taking cotrimoxazole. Check electrolytes one week after starting ACEI. Other potential adverse effects include angioedema, cough, renal insufficiency, and sexual dysfunction.

Generic Drug Name	Usual Starting Dosage/ Dosage Titration	Comments/Drug Interactions
Benazepril	Start at 10 mg QD; maximum 80 mg per day; usual dosage: 20-40 mg QD or divided BID; may need BID dosing for continuous BP control.	Start at 5 mg QD if patient is elderly, has renal insufficiency, or is taking a diuretic.
Fosinopril	Start at 10 mg QD; maximum 80 mg per day, but no additional effect over 40 mg per day; usual dosage: 10-40 mg QD or divided BID; BID dosing may be needed for continuous BP control.	Start at 5 mg QD if patient is elderly, has renal insufficiency, or is taking a diuretic.

Generic Drug Name	Usual Starting Dosage/ Dosage Titration	Comments/Drug Interactions
Lisinopril	Start at 10 mg QD; maximum 80 mg QD but no additional effect over 40 mg per day; usual dosage: 20-40 mg QD.	Start at 2.5-5 mg QD if patient is elderly, has renal insufficiency, or is taking a diuretic.
Ramipril	Start at 2.5 mg QD; maximum 20 mg QD; usual dosage: 2.5-20 mg QD or divided BID; may need BID dosing for continuous BP control.	Start at 1.25 mg QD if patient is elderly, has renal insufficiency, or is taking a diuretic.

Angiotensin Receptor Blockers (ARBs)

Pros: Cardioprotective, renal protective, first line therapy in JNC8 for non-African American population.

Cons: Avoid during pregnancy; use with caution in patients who are elderly, are fluid depleted, or have renal insufficiency. Risk of hyperkalemia. Other potential adverse effects include angioedema and renal dysfunction.

Generic Drug Name	Usual Starting Dosage/ Dosage Titration	Comments/Drug Interactions
Candesartan	Usual starting dosage: 16 mg QD, may be divided BID; maximum 32 mg per day.	Start at lower dosage in patients with moderate or worse hepatic impairment, volume depletion.
Irbesartan	Start at 150 mg QD; maximum 300 mg QD.	Start at 75 mg QD for patients with volume depletion.
Losartan	Start at 50 mg QD; maximum 100 mg QD or divided BID.	Start at 25 mg QD for patients with volume depletion or hepatic insufficiency.
Telmisartan	Usual starting dosage: 40 mg QD; maximum 80 mg QD.	Start at 20 mg QD in elderly, patients with hepatic impairment or volume depletion; monitor closely.
Valsartan	Start at 80 mg QD; maximum 320 mg QD.	-

Calcium Channel Blockers (CCBs)

Pros: CCBs may be more effective than other anti-hypertensives for African American patients.

Cons: Metabolism of CCBs is inhibited by PIs and cobicistat and its combination drugs (Stribild, Genvoya, and Prezcoibix); if CCBs must be used with PIs, reduce

initial dosage and titrate up while monitoring for side effects (e.g., hypotension, conduction block, bradycardia, and peripheral edema). Metabolism of CCBs may be induced by the NNRTIs EFV and NVP, leading to blunted antihypertensive effect.

Avoid immediate-release forms. Avoid in patients with CHF.

Generic Drug Name	Usual Starting Dosage/ Dosage Titration	Comments/Drug Interactions
Amlodipine	Start at 2.5 mg QD; maximum 10 mg daily.	See Cons above.
Diltiazem Sustained Release	Start at 60 mg BID; maximum 360 mg per day in divided doses.	
Diltiazem Extended Release	Diltiazem Extended Release	
Nifedipine Extended Release	Start at 30 mg QD; maximum 120 mg QD.	
Verapamil Sustained Release	Start at 120 mg QD; maximum 480 mg per day, but divide BID if using >240 mg per day.	Immediate-release formulation is not recommended for treatment of hypertension.
Verapamil Extended Release	Covera HS: Start at 180 mg QHS; maximum 480 mg QHS Verelan PM: start at 100 mg QHS; maximum 400 mg QHS	Immediate-release formulation is not recommended for treatment of hypertension.

Potassium-Sparing Diuretics and Aldosterone Antagonists

Pros: Indicated in CAD, and CHF with EF <40%, class IV heart failure. May be useful in patients with hypokalemia; often combined with a thiazide diuretic.

Cons: May cause hyperkalemia; monitor K+.

Generic Drug Name	Usual Starting Dosage/ Dosage Titration	Comments/Drug Interactions
Spironolactone	Usual dosage is 20 mg to 100 mg QD or divided BID.	Monitor for hyperkalemia; check K+ one week after starting spironolactone. Potential adverse effects include liver toxicity, gynecomastia, and sexual dysfunction.
Triamterene	Start at 100 mg BID; maximum daily dosage is 300 mg.	Monitor for hyperkalemia; check potassium one week after starting triamterene.

Direct Vasodilators and Anti-Adrenergic Agents

Note: Alpha-blockers used for treatment of benign prostatic hypertrophy are not recommended as monotherapy for hypertension; however, these may cause hypotension especially in patients who are taking other antihypertensive medications.

Generic Drug Name	Usual Starting Dosage/ Dosage Titration	Comments/Drug Interactions
Clonidine	PO: Start at 0.1 mg BID; increase to usual maintenance dosage of 0.2-1.2 mg divided BID to TID; maximum 2.4 mg in divided doses. Patch: Start at 0.1 mg/24-hour patch, increasing to desired effect; maximum dosage is 0.6 mg/24-hour patch.	Possible adverse effects include bradycardia, sedation. Risk of rebound hypertension upon discontinuation: taper over course of seven days.
Minoxidil	Start 5 mg QD; increase slowly every three days to effective dosage; may divide effective daily dosage BID; maximum 100 mg daily.	Possible adverse effects include pericardial effusions and tamponade. May worsen angina.
Hydralazine	Start at 25 mg BID; increase by 10-25 mg/dose to effective dosage; may divide effective daily dosage BID; maximum 200 mg per day in divided doses.	Possible adverse effects include lupus-like syndrome, requiring discontinuation (increased risk at higher dosages). May cause reflex tachycardia; use with caution in patients with CAD.
Doxazosin	Start at 1 mg QHS; maximum 16 mg per day.	Not a first-line agent. CYP3A4 Substrate; PIs may ↑. Possible adverse effects include risk of CHF, dizziness, postural hypotension, drowsiness, and syncope; all more likely if doxazosin is given with other vasodilators, including PDE 5 inhibitors. Risk of syncope with initial dosages; start at lowest dose QHS. If drug is interrupted, restart at 1 mg QHS dosing.
Prazosin	Start at 1 mg BID or TID; usual maintenance dosage 20 mg/day divided BID or TID; maximum 40 mg divided BID or TID.	Not a first-line agent. Possible adverse effects include risk of CHF, dizziness, postural hypotension, drowsiness, and syncope; all more likely if prazosin is given with other vasodilators, including PDE 5 inhibitors. Risk of syncope with initial dosage starts at lowest dose QHS.

		If drug is interrupted, restart at 1 mg QHS.
Terazosin	Start at 1 mg QHS; usual daily dosage 1-5 mg QD or divided BID; maximum 20 mg per day.	Not a first-line agent. Possible adverse effects include risk of CHF, dizziness, postural hypotension, drowsiness, and syncope; all more likely if terazosin is given with other vasodilators, including PDE 5 inhibitors. Risk of syncope with initial doses; start at lowest dosage QHS. If drug interrupted, restart at 1 mg QHS dosing.



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KEY POINTS

- At the time of HIV diagnosis, all patients should be screened for renal dysfunction with a urinalysis (UA), quantitative estimate of proteinuria, and a calculated estimate of renal function as part of a basic metabolic panel.
- Risk factors for developing kidney disease in the setting of HIV infection include: older age, female sex, African American race, hypertension, diabetes, family history of kidney disease, CD4 count below 200 cells/ μ L, unsuppressed viral load, hepatitis C virus (HCV) co-infection. All patients with HIV infection should be screened 1-2 times annually.
- Patients with HIV and chronic kidney disease (CKD) should be referred to a nephrologist in several situations, including: albuminuria over 30 mg/g creatinine in diabetics; albuminuria over 300 mg/g creatinine in non-diabetics; rapidly declining renal function, particularly in the setting of nephrotic or nephritic syndromes; or when assistance is required in managing complications of CKD, including hypertension, acidosis, anemia, or metabolic bone disease.
- CKD increases the risk of developing cardiovascular disease, which is the principal cause of mortality in patients with CKD. Cardiovascular risk factors and interventions (hyperlipidemia, hypertension, anti-platelet therapy) should be optimized as part of CKD care.
- HIV-infected patients with CKD may be less likely to receive ARV therapy, even when ARV therapy is indicated. However, the use of ARV therapy has been associated with reduction in proteinuria and improvement in renal function.
- HIV-associated nephropathy (HIVAN) is an indication to start ARV therapy and is most commonly encountered in the setting of untreated HIV infection with advanced immunosuppression. Risk factors for HIVAN include African American race, low CD4 cell count, and family history of CKD.
- African American patients with HIV are at higher risk for development of CKD and progression to ESRD, perhaps due to the inheritance of apolipoprotein L1 high-risk alleles.
- Patients with HIV infection are at increased risk for acute kidney injury (AKI) from multiple causes, including opportunistic infections, renal ischemia, volume depletion, rhabdomyolysis, urinary tract obstruction, HIV-specific glomerulopathies, and medication toxicity leading to acute tubular necrosis (ATN) (see Table 5), crystalline nephropathy, or acute interstitial nephritis (AIN).
- Medication selection and dosing for both HIV (NRTIs) and non-HIV related conditions, should take eGFR or estimated creatinine clearance into consideration (see Table 4).



BACKGROUND

HIV infection has been established as a risk factor for chronic kidney disease (CKD) and end-stage renal disease (ESRD) in the industrialized world. The preva-

Note: Some medications mentioned in this chapter may not be available on the VHA National Formulary (<https://www.pbm.va.gov/NationalFormulary.asp>). Consult VA pharmacists for alternatives.

lence and incidence of CKD in the HIV population are both expected to rise as the prevalence of HIV infection continues to increase.

- Kidney disease in patients with HIV infection may result from HIV infection itself (e.g., HIVAN, HIV-associated immune complex disease, thrombotic microangiopathy), toxicity from antiretroviral therapy (acute tubular necrosis, nephrolithiasis), development of comorbid conditions that can cause kidney disease (e.g., diabetes mellitus, hypertension, etc.), as well as the co-infection with other viruses that can contribute to kidney disease (hepatitis C). The advent of active retroviral therapy has decreased the incidence of primary HIV infection associated diseases. However, medication-related nephrotoxicity and chronic kidney diseases relating to comorbid conditions have increased. There is a high prevalence (30%) of abnormal renal function among patients with HIV disease.
- CKD is increasingly a cause of morbidity among people with HIV infection.
- African Americans are disproportionately affected by kidney disease.
- HIV-infected patients with CKD are less likely to receive ARV therapy, even when ARV therapy is indicated.
- ARV therapy should be given to patients with renal disease, if indicated, though most NRTIs must be dosed according to renal function and some ARVs should be avoided (see **Table 4** and **Table 5**).



SCREENING

- All HIV-infected patients should be screened for kidney disease:
 - at the time of HIV diagnosis;
 - at entry into VA care;
 - within 1-2 months following a change in HIV therapy; and
 - once or twice annually thereafter in the absence of additional risk factors warranting more frequent screening. More frequent monitoring may be necessary in patients with additional CKD risk factors, requiring nephrotoxic medical therapy or demonstrating progressive kidney disease.
- Patients with additional risk factors or exposure to nephrotoxic medications (including TDF) should be screened every 3-6 months.
- Screening tests of renal function should include:
 - calculated estimate of renal function such as eGFR by CKD-EPI (preferred) or MDRD or estimated creatinine clearance as calculated by the Cockcroft-Gault equation;
 - Urinalysis (UA); and
 - quantitative spot measurement of proteinuria such as the urine albumin to creatinine ratio (UACR) that is also known as urine microalbumin to creatinine ratio (UMACR).

- If screening indicates reduced creatinine clearance (CrCl) or estimated GFR (eGFR) below 60 mL/min/1.73 m², or hematuria/proteinuria on urine dipstick analysis, or spot urine albumin-to-Cr ratio greater than 30 mg/g creatinine, obtain renal ultrasound to look for anatomic abnormalities (including size and status of the collecting system—i.e., hydronephrosis).
- Consider nephrology referral for:
 - eGFR or creatinine clearance below 60 mL/min/1.73 m² for diagnostic evaluation for cause of CKD;
 - unexplained decline in renal function by more than 25% from baseline that fails to resolve after optimization of volume status, and/or removal of nephrotoxic agents;
 - albuminuria in excess of 300 mg/g creatinine in non-diabetic patients or over 30 mg/g creatinine in patients with diabetes mellitus;
 - unexplained hematuria in conjunction with albuminuria or increasing hypertension;
 - uncontrolled blood pressure despite institution of three agents including an appropriately dosed diuretic;
 - advanced chronic kidney disease (eGR below 30 mL/min/1.73 m²);
 - metabolic evaluation of recurrent renal stone disease; and
 - presence of hydronephrosis or complex cyst(s)/mass(es) on ultrasonography should also be referred to Urology.

I. Estimate renal function:

- The first detected clinical evidence of renal dysfunction is often an increase in serum creatinine (SCr) level.
- An increase in SCr from baseline should prompt an evaluation because:
 - It may indicate transient variation in renal function in response to low blood pressure, volume depletion, or medication exposures such as NSAIDs – these often respond to basic interventions. Laboratory studies should be repeated following detection and management of these concerns.
 - It may indicate non-HIV-related disease such as urinary tract obstruction; history and evaluation with renal ultrasonography may identify these concerns promptly.
- The serum creatinine level is influenced by muscle mass and, in many patients, it may not be an accurate reflection of renal function because:
 - It may be deceptively low in the elderly, cirrhotics, malnourished patients, and patients with amputations or other causes of low muscle mass.
 - It may be deceptively high in African Americans and patients with higher muscle mass.

- Most clinical laboratories will calculate an estimated GFR from the SCr in conjunction with the patient's age, sex and race, using the Modification of Diet in Renal Disease equation (MDRD) or the CKD-EPI equation.
 - **The MDRD Simplified Equation:**
 - **GFR** (mL/min/1.73 m²) = 186 × [serum creatinine (mg/dL)]^{-1.154} × [age (years)]^{-0.203} × [0.742 if female] × [1.212 if African American]
 - This formula may not provide an accurate estimation of renal function for eGFRs over 60 mL/min/1.73 m²
 - The CKD-EPI equation often outperforms the MDRD, particularly in patients with GFRs over 60 mL/min, and is the preferred equation where available. CKD-EPI equations are selected based upon the patient's sex and serum creatinine. CKD-EPI formulae are also available to calculate eGFR based on cystatin C measurements, however, as cystatin C measurements are not universally available and are not consistently standardized, the cystatin C equations are not discussed here.
 - **The CKD-EPI creatinine equations:**
 - Female, Scr ≤0.7: GFR = 144 × (Scr/0.7)^{-0.329} × (0.993)^{age} × 1.159 (if black)
 - Female, Scr >0.7: GFR = 144 × (Scr/0.7)^{-1.209} × (0.993)^{age} × 1.159 (if black)
 - Male, Scr ≤0.9: GFR = 141 × (Scr/0.9)^{-0.411} × (0.993)^{age} × 1.159 (if black)
 - Male, Scr >0.9: GFR = 141 × (Scr/0.9)^{-1.209} × (0.993)^{age} × 1.159 (if black)
- Alternatively, the Cockcroft-Gault equation estimates creatinine clearance, a surrogate measurement for GFR, and is frequently used to estimate renal function for the purposes of medication dose adjustment. While typically the least accurate or precise of the prediction formulae, it may be useful for older and cachectic patients and is traditionally used by FDA for renal drug dosing adjustments.
 - **The Cockcroft-Gault equation**
 - CrCl = {[(140-age) × weight (kg)]/72 × SCr} × 0.85 (if female)
- All of these equations assume that:
 - the patient is at steady state;
 - the patient has normal muscle-mass for their age, sex, and race.
- If these conditions are not met, clinical judgment or direct measurement of GFR may need to be considered.
 - **Simplified MDRD Equation for Estimating Renal Function:**
 - The National Institute of Diabetes and Digestive and Kidney Diseases hosts an online calculator for creatinine standardization. Visit <https://www.niddk.nih.gov> for details.

2. **Perform urinalysis (dipstick or formal);** look especially for proteinuria and hematuria.

Table 1. Dipstick Interpretation in Setting of Abnormal eGFR

Protein	Blood	Consider
Negative	Negative	Microalbuminuria (see below), multiple myeloma and other paraproteinemias, prerenal (including NSAIDs and renin angiotensin system inhibitors) or postrenal causes for renal insufficiency (see Table 3). Falsely negative measurements may occur, particularly in dilute urine (specific gravity below 1.005).
Positive	Negative	Benign or orthostatic proteinuria, hypertension, nephrosclerosis, diabetic nephropathy, tubulointerstitial diseases, polycystic kidney disease (PCKD), nephrotic syndromes including HIV-associated nephropathy (HIVAN). Falsely positive measurements may occur, particularly in concentrated urine (specific gravity over 1.025).
Positive	Positive	UTI including pyelonephritis, glomerulonephritis (GN, including rapidly progressive GNs, HIV-associated immune complex disease or vasculitis, pulmonary-renal syndromes, hemolytic-uremic syndrome, thrombotic thrombocytopenic purpura, malignant hypertension, nephrolithiasis with obstruction, atypical diabetes, PCKD.

3. **Quantitate proteinuria:**

- Urine albumin to creatinine ratios (UACRs) as known as urine microalbumin assays (UMACRs) should be performed on all patients with HIV infection because:
 - Albuminuria below the detection threshold of the dipstick, also known as microalbuminuria, may be the first indication of renal dysfunction. The dipstick UA is insensitive for albumin concentrations below 15-30 mg/dL and may read negative in this setting.
 - The dipstick UA can be falsely positive for protein in the setting of concentrated urine.
- The dipstick UA can be falsely negative for protein in the setting of dilute urine. Timed (i.e., 24-hour) collections have largely been replaced by:
 - The **random urinary albumin-to-Cr ratio (UACR):** $\text{Albumin}_{\text{Urine}} \text{ [mg/dL]} / \text{Cr}_{\text{Urine}} \text{ [mg/dL]}$
 - Highly sensitive for microalbuminuria; normal is below 0.03 mg/mg creatinine or 30 mg/g creatinine.
 - Should be used at initial screening and for follow-up, if microalbuminuria is diagnosed.

- The **random urinary protein-to-Cr ratio (UPCR):** $\text{Protein}_{\text{Urine}} [\text{mg/dL}] / \text{Cr}_{\text{Urine}} [\text{mg/dL}]$
 - Highly sensitive for proteinuria, but not specific for microalbuminuria; normal is $<0.15 \text{ mg/mg}$. Unlike the dipstick and urinary albumin quantitation, the UPCR will detect all urinary proteins including tubular proteins and paraproteins in addition to albumin and can be used to estimate 24-hour urine protein excretion.

Note: these estimates using the urine creatinine may be inaccurate in muscular or cachectic patients.

Degree of Proteinuria Based on Spot Urinary Protein-to-Cr Ratio

- Normal: $<150 \text{ mg/24 hours}$
- Trace proteinuria: $150\text{-}500 \text{ mg/24 hours}$
- Mild proteinuria: $500 \text{ mg to } 1 \text{ g/24 hours}$
- Moderate proteinuria: $1\text{-}3 \text{ g/24 hours}$
- Nephrotic range proteinuria: $>3.5 \text{ g/24 hours}$
- Patients with mild or greater proteinuria should be referred for further evaluation.

Types of Proteinuria

- **Overflow proteinuria:** Trace or negative dipstick protein but disproportionately larger amount on 24-hour test or UPCR may suggest light-chain disease, paraproteinemia, lymphoproliferative process, or hemolysis (if dipstick is also positive for blood).

Differentiate tubular causes from glomerular causes by urine protein electrophoresis (UPEP) +/- immunoelectrophoresis.

- UPEP: albumin $>$ globulin suggests glomerular proteinuria; globulin $>$ albumin suggests light chains or paraproteinemia

Common causes of tubular proteinuria include analgesic nephropathy, focal glomerular sclerosis (recurrent UTI, reflux), collagen vascular diseases (Sjögren syndrome, lupus), hepatitis, HIVAN (see below), PCKD, heavy metal toxicity, interstitial nephritis (drugs or infectious), granulomatous diseases.

- **Glomerular protein, suggested by moderate to heavy proteinuria:** Suggests a more serious disorder. Rule out HIVAN, diabetes progression, hepatitis, vasculitis, malignancy, GN.
- Proteinuria of $>3.5 \text{ g}$ suggests significant glomerular damage and should be referred for nephrologic evaluation.

Massive proteinuria: $>6 \text{ g/24 hours}$

Focus evaluation on glomerular disease, including HIVAN, hepatitis-associated nephropathy, focal glomerulosclerosis (FSGS) or other glomerulonephropathies. Refer to nephrologist.

Chronic Kidney Disease



EVALUATION

- CKD is characterized by the presence of either of the following **for at least 3 months, with implications for future health.**
 - Structural or functional kidney abnormalities, such as proteinuria, upper tract hematuria, stones, or reduced nephron mass, with or without decreased GFR.
 - GFR or eGFR below 60 mL/min/1.73 m², with or without other evidence of kidney damage (see **CKD-EPI** and simplified **MDRD** equations, above).
- Proteinuria and eGFR below 60 mL/min/1.73 m² are associated with increased cardiovascular disease and increased all-cause mortality.
- Treatment of early-stage CKD, including diagnosis, control of BP, reduction in proteinuria, and medication review to include removal and avoidance of nephrotoxic agents, can slow progression of kidney disease as well as identify potentially treatable or reversible causes of kidney disease.
- CKD has 5 stages, based on estimated renal function (see **Table 2**).

Table 2. National Kidney Foundation Stages of Chronic Kidney Disease (based on eGFR)

Stage	Definition	eGFR (mL/min/1.73 m ²)	Recommendations
1	Kidney damage with normal eGFR	≥90	Treat comorbid conditions; slow progression of CKD; reduce cardiovascular risk factors
2	Kidney damage with mildly decreased eGFR	60-89	Estimate progression of CKD
3	Kidney damage with moderately decreased eGFR	30-59	Evaluate and treat complications of CKD
4	Kidney damage with severely decreased eGFR	15-29	Prepare for renal replacement therapy (RRT; dialysis)
5	Kidney failure*	<15*	RRT, if uremia present*

*Dialysis for ESRD is initiated for development of symptomatic uremia, or complications of CKD refractory to medication or dietary management rather than a specific level of eGFR.

The staging of CKD has also been modified to include albuminuria quantitation as patients with preserved renal function and heavy proteinuria have shown increased risk of progression. Current staging of CKD therefore includes a G (GFR) component – as summarized above and an A (albuminuria) component.

Prognosis of CKD by GFR and Albuminuria Category

Prognosis of CKD by GFR and Albuminuria Categories: KDIGO 2012				Persistent albuminuria categories		
				Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30mg/g <3 mg/mmol	30-300 mg/g 3-30 mg/mmol	>300 mg/g >30 mg/mmol
GFR categories (ml/min/1.73m ²) Description and range	G1	Normal or high	≥90	†	◊	+
	G2	Mildly decreases	60-89	†	◊	+
	G3a	Mildly to moderately decreased	45-59	◊	+	*
	G3b	Moderately to severely decreased	30-44	+	*	*
	G4	Severely decreased	15-29	*	*	*
	G5	Kidney failure	<15	*	*	*

† Green, low risk (if no other markers of kidney disease, no CKD); ◊ Yellow, moderately increased risk; + Orange, high risk; * Red, very high risk.

Evaluation of CKD

Risk Factors	<ul style="list-style-type: none"> • Diabetes • Hypertension • Toxic insults (including medications such as NSAIDs, tenofovir disoproxil fumarate, atazanavir) • Autoimmune disease (such as SLE) • HCV infection • Inherited kidney disease (e.g., Polycystic Kidney Disease) • HIVAN (see below) • Chronic urinary tract obstruction • Paraproteinemias • Prior episodes of AKI • Chronic Lead Exposure
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History	<ul style="list-style-type: none"> • Chronic medical problems: diabetes, hypertension, prior kidney disease, collagen vascular disease, hepatitis, kidney stones, prostate disease • Occupational exposures • Symptoms associated with uremia such as: decreased attentiveness, nausea, vomiting, anorexia, fatigue, muscle cramps, restless legs, peripheral neuropathy, pruritus, urinary urgency or frequency, nocturia, dysuria, oliguria • Symptoms relating to volume overload or depletion such as: weight change, dyspnea, orthopnea, leg swelling, orthostasis, dizziness • Medications and over-the-counter products: NSAIDs, ACE inhibitors (ACEIs), angiotensin receptor blockers (ARBs), diuretics, analgesics, antibiotics, antiviral agents, lithium
Physical Examination	<ul style="list-style-type: none"> • Height, weight • Vital signs including orthostatic blood pressure • Volume assessment (rales, jugular venous distention, peripheral edema) • Cardiac exam (S3, S4, heave, murmur, rub) • Vascular exam (pulses, bruits) • Abdominal findings (mass, bruit, palpable bladder, flank tenderness) • Digital rectal exam (prostate) in men • Neurological exam, including mental status • Integument (rash, stigmata of embolic disease or ischemia) • Joints (arthritis)
Diagnostic Testing	<ul style="list-style-type: none"> • eGFR, urinalysis, spot urine albumin-to-Cr ratio or protein-to-Cr ratio, as above • Renal ultrasound • Basic workup for non-HIV-related causes: <ul style="list-style-type: none"> • Hepatitis B and C serologies • Fasting blood glucose • Complement levels • Antinuclear antibodies and anti-neutrophil cytoplasmic antibodies <p>(Note: significant false-positive rates in HIV-infected patients)</p>



WHEN TO REFER

- Patients may be referred to nephrologist for:
 - diagnosis when eGFR below 60 mL/min/1.73 m²;
 - co-management of CKD complications and preparation for renal replacement therapy

- rapy when eGFR falls below 30 mL/min/1.73 m²;
- evaluation of AKI, heavy proteinuria or suspected glomerulonephritis; and
- metabolic evaluation of recurrent stone disease.
- Patients with heavy proteinuria, hematuria/proteinuria in combination, rapidly declining renal function or accelerated hypertension should be referred to nephrology more urgently for evaluation of glomerulonephritis and consideration of kidney biopsy, particularly if HIVAN is suspected.
 - HIVAN can progress rapidly from proteinuria to end-stage renal disease (ESRD), and requires biopsy for diagnosis. See **HIV-Associated Nephropathy**, below.
 - Kidney biopsy also can identify other HIV-related causes of CKD, such as immune complex disease and thrombotic microangiopathy, as well as non-HIV-related causes of CKD.

Rx MANAGEMENT

Key Goals

- **Slow progression of CKD**
- **Address metabolic and hematologic abnormalities associated with CKD**
- Control hypertension
 - Patients with HIV infection and CKD but without significant albuminuria, i.e. less than 30 mg/g creatinine, should have BP controlled to below 140/90 as tolerated without adverse effects.
 - Patients with HIV, CKD and albuminuria greater than 30 mg/g creatinine, should have BP controlled to below 130/80 as tolerated without adverse effects.
- In patients with hypertension and albuminuria greater than 30 mg/g creatinine, ACE inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) should be preferentially used to control BP and reduce proteinuria. The combination of ACEI with ARB therapy has been shown to result in significant complications such as hyperkalemia and hypotension – and should be avoided. ACEI and ARB are category X agents in pregnancy. See **Hypertension**, p. 479, for dosing information.
- Closely monitor patients on ACEIs and ARBs for hyperkalemia. Initiation and dose adjustment of these medications should be accompanied by laboratory monitoring for hyperkalemia, and it may be necessary to counsel patients on a low potassium diet, stop potassium supplements, or institute concurrent diuretic therapy to allow treatment with the agents. Medications such as trimethoprim-sulfamethoxazole (TMP-SMX), spironolactone, eplerenone, triamterene, and amiloride may increase the risk of hyperkalemia when these agents are prescribed and patients will require close monitoring or medication adjustment in these settings.
- ARV therapy:

- Initiate or maximize efficacy of ARV therapy if diagnosis of HIVAN is established (see below).
- Avoid ARV therapies with significant renal toxicity. See **Selecting ARV Therapies for Patients with Kidney Disease**, below.
- Adjust dosing of ARV therapies (see below) and other drugs (e.g., TMP-SMX, H2 receptor antagonists) for renal function, as needed.
- Avoid NSAIDs and other nephrotoxic medications.
- Screen for and/or maximize treatment for dyslipidemia and cardiovascular disease prevention (See **Dyslipidemia**, p. 417).
 - Consider statin treatment in patients with HIV and CKD to prevent cardiovascular disease in patients with greater than 7.5% 10-year risk of CVD.
 - Consider prescription of low dose (75-100 mg daily) aspirin for cardiovascular disease prevention. Benefits of aspirin should be balanced against the individual's risk for bleeding.
- Optimize diabetes control and prevention. (See **Diabetes Mellitus**, p. 397).
- Screen for and treat hematologic abnormalities (e.g., anemia).
 - Periodically monitor iron studies and ferritin in patients with CKD G3 or worse and anemia, i.e. hgb below 13 g/dL. Evaluate and treat iron deficiency including consideration of evaluation for GI bleeding and replacement of iron with oral iron salts.
 - Erythropoiesis-stimulating agents (ESAs) have been associated with adverse effects such as hypertension, venous thromboses, stroke, and increased cancer-related mortality in patients with malignancy, and should therefore be used with caution to prevent transfusion when hemoglobin levels are below 10 g/dL in patients with anemia due to advanced CKD. Anemia in CKD requiring ESA use is uncommon in patients with eGFR better than later stage 4 CKD and other causes for anemia should be pursued in this setting.
- Advise patients with hypertension and/or proteinuria, on a salt-restricted diet. Medications enhancing potassium and phosphorus excretion may be necessary in patients with elevated serum or plasma levels of these minerals. Patients may be referred to renal dietitian for further education and to avoid malnutrition as dietary restrictions become more complicated.
- Refer for substance abuse counseling, when appropriate; IV recreational drugs can increase the risk of acquiring additional chronic viral infections as well as other renal/glomerular diseases. Tobacco smoking may contribute to glomerular disease and patients should be counseled to quit smoking for this reason and to decrease cardiovascular risk. Patients with substance abuse concerns must successfully complete substance abuse counseling in order to be considered for renal transplantation.

- **If not already followed by nephrology, refer patients with advanced CKD (eGFR below 30 ml/min/1.73m² for co-management of complications of chronic kidney disease, and preparation for renal replacement therapy (RRT) or kidney transplantation.**
 - Advanced preparation (ex. as eGFR approaches 20 mL/min/1.73 m²) for ESRD including education on RRT modalities and referral for dialysis access placement for RRT can improve outcomes.
 - HIV-infected patients may be eligible for kidney transplant when the eGFR is less than or equal to 20 ml/min/1.73 m².
 - HIV-infected and HIV-uninfected ESRD patients have similar outcomes.

Transplant Evaluation

Referral for transplant evaluation may be made to the VA National Transplant Program at <https://www.va.gov/health/services/transplant/>. Please consult with the relevant transplant program for specific transplant eligibility requirements. In general, patients should not have active malignancy, untreated infection, or advanced dementia in order to be considered for evaluation. HIVAN (HIV-Associated Nephropathy)



EVALUATION

- HIVAN occurs most commonly in patients of African descent. Other risk factors include low CD4 cell count and high HIV viral load.
- Much less common since more widespread use of combination ARV therapy.
- Among African American men, between 1995 and 1999, incidence of HIVAN decreased whereas prevalence and survival increased, which is consistent with a beneficial effect of ARV therapy on preventing and treating HIVAN.
- Most often presents as nephrotic syndrome, with proteinuria, edema and decreased GFR. May progress rapidly to ESRD, often over weeks to months, particularly in patients not taking ARV therapy.
- Renal ultrasonography typically shows large echogenic kidneys.
- Biopsy shows collapsing focal segmental glomerulosclerosis with tubular and interstitial damage.

- All patients with HIVAN should be started on ARV therapy regardless of CD4 count.
- Refer promptly to a nephrologist for evaluation (potentially including renal biopsy) and consideration of adjunctive treatment in addition to ARV therapy, such as corticosteroids. HIVAN in adults may respond to high dose (1 mg/kg daily, maximum dose 80 mg daily) corticosteroid therapy in addition to ARV therapy.
- For patients with hypertension or proteinuria, treatment with ACEIs or ARBs is also indicated to reduce proteinuria and control blood pressure to below 130/80 mmHg.

Patients with progressive disease should be referred for advanced CKD care as above.

Acute Kidney Injury



BACKGROUND

- Definitions of AKI:
 - Several definitions of acute renal failure (ARF) or acute kidney injury (AKI) have appeared in the HIV and nephrology literature over the past 20 years.
 - The Kidney Disease Improving Global Outcomes (KDIGO) collaborative group defines AKI as any of the following:
 - Increase in SCr by ≥ 0.3 mg/dl (≥ 26.5 $\mu\text{mol/l}$) within 48 hours.
 - Increase in SCr to ≥ 1.5 times baseline, which is known or presumed to have occurred within the prior 7 days.
 - Urine volume < 0.5 mL/kg/h for 6 hours. Patients with HIV have been shown to be at higher risk of sustaining an AKI.
 - In a prospective cohort of HIV-infected outpatients, incidence of AKI was 5.9 cases per 100 person-years. The most common causes of AKI were a prerenal state and acute tubular necrosis (ATN).
 - A prospective study of 754 HIV-positive patients followed at a single center revealed 111 episodes of AKI in 71 patients over a two-year period with the principal causes identified as:
 - Pre-renal states (volume depletion, heart failure, cirrhosis) – 39%;
 - Acute tubular necrosis (ischemic and nephrotoxic) – 37%;
 - Crystalluria with obstruction – 5%;
 - Interstitial nephritis – 5%.

RISK FACTORS

- Male sex
- HCV co-infection
- HIV viral load >10,000 copies/mL
- CD4 count <200 cells/ μ L
- Presence of an opportunistic infection
- History of an AIDS diagnosis
- Current or prior ARV therapy
- Non-HIV-related risk factors
 - Diabetes mellitus
 - Older age
 - Pre-existing CKD
 - Liver disease
- AKI may present as an asymptomatic increase in serum creatinine, as volume depletion with hypotension, and postural dizziness, acute urinary tract obstruction, findings suggestive of glomerulonephritis, or may present with symptoms of renal insufficiency including volume overload (dyspnea, orthopnea), hypertension, metabolic abnormalities, or uremic symptoms, including anorexia, nausea, vomiting, or encephalopathy.



EVALUATION

- Obtain targeted history and physical examination investigating symptoms and causes below. Evaluation should include vital signs with comparison to prior blood pressures to exclude relative hypotension as well as careful review of medications including recent medication changes, new medications, over the counter medications, and dietary supplements.
- Obtain serum electrolytes, complete blood counts, urinalysis, and consider renal ultrasound.

Table 3. Possible Causes of AKI

Prerenal Causes	<ul style="list-style-type: none">• Hypovolemia: hemorrhage, volume depletion attributable to diarrhea, vomiting, or inadequate fluid intake• Hypoperfusion: ischemia (septic shock, heart failure, cirrhosis, cardiogenic shock); reduced oncotic pressure (hypoalbuminemia, anemia)
Intrinsic Renal Causes	<ul style="list-style-type: none">• Glomerulonephritis (any type)• ATN resulting from prolonged prerenal injury• ATN resulting from toxins, including nephrotoxic medications:

	<p>IV radiographic contrast dye, pentamidine, amphotericin B, foscarnet, cidofovir, high-dose acyclovir, aminoglycosides, TDF</p> <ul style="list-style-type: none"> • ATN resulting from rhabdomyolysis (crush injury, statins [including in association with PIs], fibrate derivatives, cocaine) • Acute interstitial nephritis (AIN) resulting from medications: TMP-SMX and other sulfa-containing compounds, beta-lactam • antibiotics, rifampin, indinavir, NSAIDs, salicylates, PPIs, many other medications • AIN resulting from infection: streptococcus, cytomegalovirus (rare) • Vascular insults such as embolism, thrombotic thrombocytopenic purpura, or hemolytic-uremic syndrome
Postrenal Causes	<ul style="list-style-type: none"> • External obstruction: retroperitoneal masses; ureteral compression, urethral compression or blockage (e.g., severe benign prostatic hypertrophy) • Internal obstruction: intratubular crystal deposition, nephrolithiasis, clot

Rx MANAGEMENT

- Assess volume status and metabolic abnormalities.
- Address any underlying processes that are contributory or causative to the AKI (i.e. sepsis, nephrotoxic medications, etc.).
- Provide supportive care for symptoms and complications of AKI including renal replacement therapy if indicated.
- Renal replacement therapy may be indicated for uremic pericarditis, encephalopathy, as well as volume overload, hyperkalemia, or metabolic acidosis that are refractory to medical management.

Selecting ARV Therapies for Patients with Kidney Disease

- ARV therapy generally should **not** be avoided because of kidney disease.
- ARV therapy is indicated in patients with HIVAN.
- Accumulating evidence suggests ARV therapy decreases the risk of kidney disease in HIV-infected patients.
- NRTIs, except abacavir (ABC), are excreted renally; dosage should be prescribed based on steady-state CrCl or eGFR. See **Table 4**.
- Tenofovir disoproxyl fumarate (TDF) has been associated with rare cases of ARF and Fanconi syndrome (a syndrome of inadequate reabsorption in the proximal renal tubules, resulting in polyuria, polydipsia, acidosis, osteomalacia, acidosis, hypokalemia, proteinuria, hypophosphatemia/hyperphosphaturia, glycosuria, and hyperuricosuria).

- TDF also has been associated with slow decreases in eGFR, typically in patients with preexisting renal insufficiency. See **Table 5**.
- Agents from other classes (NNRTI, PI, fusion inhibitor, integrase inhibitor, chemokine co-receptor antagonist) do not undergo significant renal excretion and do not require dosage adjustment in patients with renal insufficiency.
- For patients undergoing hemodialysis:
 - Serum levels of the ATV and LPV, are substantially decreased in patients on hemodialysis for unclear reasons.
 - Unboosted ATV should not be given, and neither ATV/r nor ATV/cobicistat should be given to HIV treatment-experienced patients.
 - LPV/r should not be given QD, and LPV levels may be too low for those patients with resistance mutations to LPV, but still are not considered to have genotypic resistance to LPV/r.
 - Other PIs have not been well studied in hemodialysis.
 - Nevirapine: Give an additional dose (200 mg) after each dialysis session.
- IDV and (rarely) ATV have been associated with nephrolithiasis. See **Table 5**.
- Note that other medications commonly given to HIV-infected patients may also cause renal dysfunction. See **Table 5**.

Table 4. NRTI Dosing for Patients with Decreased Renal Function (based on CrCl)

Drug	Standard Dosage	Adjusted Dosage/Notes		
ABC	300 mg PO BID	Dosage adjustment for renal insufficiency does not appear necessary		
ddl	250-400 mg PO QD, depending on weight	CrCl (mL/min)	Weight ≥60 kg	Weight <60 kg
		≥60	400 mg QD	250 mg QD
		30-59	200 mg QD	125 mg QD
		10-29	125 mg QD	125 mg QD
		<10	125 mg QD	formulation not suitable
		Hemodialysis	125 mg QD	formulation not suitable
FTC	200 mg PO QD	CrCl (mL/min)		
		≥50	200 mg QD	
		30-49	200 mg Q48H	

Drug	Standard Dosage	Adjusted Dosage/Notes	
-	-	15-29	200 mg Q72H
		<15	200 mg Q96H
		Hemodialysis	200 mg Q96H, give after dialysis
3TC	150 mg PO BID or 300 mg PO QD	CrCl (mL/min)	
		≥50	150 mg BID or 300 mg QD
		30-49	150 mg QD
		15-29	150 mg first dose, then 100 mg QD
		5-14	150 mg first dose, then 50 mg QD
		<5	50 mg first dose, then 25 mg QD

Adapted from McNicholl IR, Rodriguez RA. Dosing of Antiretroviral Drugs in Adults with Renal Insufficiency and Hemodialysis. San Francisco: University of California San Francisco, Center for HIV Information; 2010. Available at: <http://hivinsite.ucsf.edu>. Accessed April 1, 2011.

ARV Therapy and Other Medications Associated with Renal Dysfunction

A number of medications commonly prescribed for treatment of HIV infection or opportunistic illnesses may cause acute or chronic renal disease. See **Table 5**. Some of these should be avoided in patients with renal insufficiency.

Table 5. Renal Adverse Effects of Medications Commonly Taken by HIV-Infected Patients

Drug	Disorder/ Pathology	Findings	Comments/Suggestions
TDF	TDF-associated renal insufficiency	↑ Cr, usually small; slight (4% vs. other NRTIs) decrease in eGFR over time	<ul style="list-style-type: none"> Tenofovir disoproxil fumarate is a known nephrotoxin and warrants close monitoring of renal function. If possible, TDF should be avoided with steady-state eGFR below 70 ml/min and stopped if steady state eGFR falls below 50 mL/min. May be associated with duration of HIV infection, concomitant RTV-boosted PIs (which boost TDF levels), preexisting renal dysfunction, or diabetes.

Drug	Disorder/ Pathology	Findings	Comments/Suggestions
-	-	-	<ul style="list-style-type: none"> • Check serum and urine electrolytes, eGFR, and UA before starting therapy; check serum electrolytes and eGFR every 3-6 months on TDF; check UA every 6 months. • Development of hypokalemia, metabolic acidosis, and/or hypophosphatemia are suggestive of proximal tubule toxicity and should prompt re-consideration of ARV therapy. • Consider more frequent monitoring in patients with eGFR ≤ 90 mL/min/1.73 m², renally secreted drugs, RTV-boosted PIs, diabetes or hypertension.
	Proximal tubular injury (ATN) Fanconi syndrome	metabolic acidosis	<ul style="list-style-type: none"> • Adjust TDF dosage based on steady-state CrCl or eGFR. • AKIs may resolve with discontinuation of TDF, but continued use may lead to permanent damage, ESRD.
	Nephrogenic diabetes insipidus (rare)	\uparrow Cr, \downarrow serum K ⁺ and phosphate, \uparrow urine bicarbonate, phosphate, glucose	<ul style="list-style-type: none"> • Renal insufficiency with TDF may be more likely in patients with pre-existing renal disease.
	Acute interstitial nephritis	polyuria, excessive thirst; \uparrow plasma osmolarity; \downarrow urine osmolarity	<ul style="list-style-type: none"> • Check serum and urine electrolytes, eGFR, UA before starting therapy and every 3-6 months on therapy, especially in patients with eGFR ≤ 90 mL/min/1.73 m², renally secreted drugs, RTV-boosted PIs (which also boosts TDF levels), diabetes, or hypertension.
ATV	Nephrolithiasis Crystalline-associated AKI Acute interstitial nephritis	Symptoms of renal colic, dysuria, urgency; mild \uparrow Cr ATV-containing stones	<ul style="list-style-type: none"> • ATV has been associated with AKI and radiolucent stone disease in case reports. • Symptomatic stones require urologic assessment and may be treated with hydration; if symptoms do not resolve, or if symptoms recur, may require urologic intervention and may need to discontinue drug.

Drug	Disorder/ Pathology	Findings	Comments/Suggestions
IDV	AIN	↑ Cr, pyuria	<ul style="list-style-type: none"> Usually resolves with drug discontinuation; may require steroids.
	Crystalluria Crystalline-associated AKI	Asymptomatic, or symptoms of renal colic, dysuria, urgency; crystals on UA; mild ↑ Cr	<ul style="list-style-type: none"> Treat with hydration. If manifestations do not resolve, may need to discontinue drug. Not necessary to discontinue for asymptomatic crystalluria.
	Nephrolithiasis	Renal colic, dysuria, urgency; mild ↑ Cr; crystals on UA; stones or filling defects on radiography	<ul style="list-style-type: none"> Risk reduced by drinking. 1.5-2 liters of liquids per day. Treat with hydration; if symptoms do not resolve, or if symptoms recur, may need to discontinue drug.
Amphotericin B	Increased tubular permeability and/or renal vasoconstriction. Distal renal tubular acidosis	↑ Cr, ↓ serum K ⁺ and Mg ⁺⁺ , ↓ urine bicarbonate; distal renal tubular acidosis; non-anion-gap metabolic acidosis	<ul style="list-style-type: none"> More severe renal failure likely when administered with concurrent nephrotoxins (aminoglycosides, foscarnet), diuretic use, hypovolemia, or CKD. Hydration with normal saline may provide some renal protection. Switch to lipid formulation of amphotericin B for rise in Cr of >2.5 mg/dL while on conventional amphotericin B; continue to monitor electrolytes. May also consider use of lipid formulations of amphotericin B in patients at elevated risk for AKI.
Cidofovir	Proximal tubular injury	See TDF , above.	<ul style="list-style-type: none"> Incidence reduced with hydration (normal saline) and probenecid, which blocks absorption of drug by tubular epithelial cells. Check Cr and urine protein within 48 hours before each dose and reduce dosage for

Drug	Disorder/ Pathology	Findings	Comments/Suggestions
-	-	-	<p>decreased CrCl or eGFR.</p> <ul style="list-style-type: none"> Discontinue drug for either Cr ≥ 0.5 mg/dL above baseline or proteinuria $\geq 3+$ on dipstick analysis.
Foscarnet	ATN Crystal depo- sition	\uparrow Cr, \downarrow serum Ca $^{++}$, Mg $^{++}$, phos- phorus; sometimes \uparrow serum Ca $^{++}$ and phosphorus	<ul style="list-style-type: none"> Cr generally increases after 1-2 weeks of foscarnet therapy. Renal toxicity is reduced with infusion of 0.5-1 liter of normal saline with or before foscarnet. Toxicity is more likely with concomitant nephrotoxins.
Pentami- dine (IV, rarely aerosol- ized)	Tubular toxic- ity (ATN)	\uparrow Cr, \uparrow serum K $^{+}$; \downarrow serum Mg $^{++}$ and Ca $^{++}$	<ul style="list-style-type: none"> Discontinuation of pentamidine reverses toxicity, although that process can take several weeks.
TMP-SMX	Hyperka- lemia and mild diuresis caused by blockage of epithelial Na $^{+}$ channel in collecting tubule. Impaired tubular secre- tion of Cr. Bone marrow suppression due to accu- mulated drug in reduced GFR states.	\uparrow Serum K $^{+}$ \uparrow Cr Anemia Leukopenia Pancytopenia	<ul style="list-style-type: none"> Usually seen with high-dose therapy (e.g., PCP treatment), but sometimes seen with lower dosages. Hyperkalemia more common with preexisting renal insufficiency. Hyperkalemia often appears after 1 week of therapy. Consider monitoring serum K$^{+}$, especially with high-dose therapy. Use with caution when co-prescribed with ACE inhibitors, ACE receptor blockers, spironolactone, eplerenone, amiloride, triamterene, or KCl. Trimethoprim requires dose adjustment for steady state eGFR. Should be avoided in patients on dialysis if possible.

Renal Effects of Newer Antiretroviral Agents

In 2016, tenofovir alafenamide (TAF) entered the market as a component of three combination antiretrovirals: descovy (TAF, emtricitabine (FTC), genvoya (TAF, FTC, elvitegravir-cobicistat) and odefsey (TAF, FTC, rilpivirine). TAF is a novel prodrug of tenofovir, with reduced adverse effects on renal func-

tion and bone metabolism as compared to TDF. TAF-containing products are FDA-approved to be given without dose adjustment down to a CrCl of 30 mL/min. Unlike TDF, TAF has not been shown to cause Fanconi syndrome. Also, for patients with proteinuria on TDF-containing regimens, a switch to TAF-FTC-elvitegravir-cobicistat results in decreased levels of proteinuria. Because of lesser bone and renal toxicity, many practitioners are transitioning patients from TDF-containing regimens to TAF-containing medications.

Two combination antiretroviral drugs contain the pharmacologic booster cobicistat (COBI), Stribild (TDF-emtricitabine-COBI-elvitegravir) and Genvoya (TAF-emtricitabine-COBI-elvitegravir). COBI inhibits a transporter on the tubule cells that induces the efflux of creatinine into the urine. Thus, COBI decreases apparent CrCl but has no effect on GFR. However, co-administration of TDF and COBI results in a 25–30% increase in the area under the curve of the former by increasing the intestinal absorption of TDF by inhibition of P-glycoprotein. This can result in an increase in adverse renal effects for patients on Stribild. Patients with an increase in serum creatinine when initiated on Stribild require careful monitoring of renal function. An early low-level increase in serum creatinine is likely to be due to the effect of COBI on creatinine secretion alone and does not require drug cessation, but must be distinguished from actual effects of Stribild on GFR. See **Table 6**.

The three integrase inhibitors have differing effects on renal function. Raltegravir has mild effects on tubular and glomerular function, causing an average increase in creatinine of 0.1 mg/dL. Dolutegravir inhibits OCT2 transporter of the proximal tubule resulting in an average increase of creatinine of 0.14 mg/dL. Elvitegravir has minimal influence on renal function. The renal effects of all of these newer antiretroviral agents are detailed in **Table 7**.

Table 6. Distinguishing the effects of antiretrovirals on tubular creatinine secretion from drug-induced nephrotoxicity

Inhibition of Tubular Creatinine Secretion	Drug-induced Nephrotoxicity
Increase in serum creatinine of up to 0.23 mg/dL or decrease in eGFR of <24 mL/min	No limit to increase in serum creatinine
Change in serum creatinine or eGFR always occurs within 4 weeks of drug therapy	Change in serum creatinine or eGFR can occur at any time after drug initiation
Change in serum creatinine or eGFR is non-progressive	Change may be progressive (but not always)
No proteinuria	Low-level proteinuria is common

No change in serum electrolytes

May have full or partial Fanconi syndrome with phosphaturia, hypophosphatemia, mild acidosis, and normoglycemic glycosuria

Table 7. Summary of Effects of Newer Antiretroviral Drugs on Renal Function

Medication	Effect on Tubule	Effect on Glomerulus	Magnitude of Effect	Mechanism
Raltegravir	Yes	Yes (small)	crt increase 0.1 mg/dL; GFR decrease 8.5 mL/min/1.73 ²	Unknown
Dolutegravir	Yes	No	crt increase of 0.14 mg/dL	inhibits OCT2 of proximal tubule
Elvitegravir	No	No	-----	-----
Cobicistat	Yes	No	decrease eGFR of 14.3 mL/min/1.73m ²	Inhibits MATE1 of proximal tubule
TAF	No	Yes (small)	Mild decrease eGFR	ATN

OCT2 = organic cation transporter 2; MATE1 = multidrug and toxin extruder protein 1.



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Sexually Transmitted Infections (STIs)

KEY POINTS

- STIs are a major health problem.
- STIs are acquired by having unprotected vaginal, anal, or oral sex.
- The majority of STIs are asymptomatic hence surveillance is paramount.
- Early diagnosis and treatment of STIs are very important.
- STIs can increase the risk for a patient who is HIV-negative of becoming infected with HIV and a patient who is HIV-positive of transmitting HIV to someone else.



BACKGROUND

There is a global epidemic of sexually transmitted illnesses (STIs). The World Health Organization (WHO) estimates more than 1 million STIs are acquired every day worldwide. The incidence of syphilis, gonorrhea, and *Chlamydia* diagnoses reported nationally reached an all-time high in 2016 of more than 2 million cases. CDC estimates that more new infections occur in the U.S. annually, close to 20 million. The increase is the highest in men who have sex with men (MSM), men who have sex with men and women (bisexual) men, women, and infants.

Syphilis (primary and secondary), urogenital gonorrhea, and urogenital chlamydia may be more prevalent among MSM who are HIV-positive than among MSM who are HIV-negative.

Transmission of HIV is increased by the presence of STIs, so active screening in HIV-negative individuals who are at increased risk of STIs is paramount for HIV prevention.

The most common STIs and the infecting pathogens are:

- Genital warts (human papilloma virus, multiple strains)
- HIV (HIV virus)
- Syphilis (*Treponema pallidum*)
- Gonorrhea (*Neisseria gonorrhoea*)
- Chlamydial infections (*Chlamydia trachomatis*)
- Trichomoniasis (*Trichomonas vaginalis*)
- Genital herpes simplex virus (HSV) Infections (HSV-2 in 70-80%, HSV-1 in 20-30%)
- Lymphogranuloma venereum (*C. trachomatis* serovars L1, L2, L3) Hepatitis B (hepatitis B virus)
- Hepatitis C infection among MSM who are HIV-positive (hepatitis C virus)

Note: Some medications mentioned in this chapter may not be available on the VHA National Formulary (<https://www.pbm.va.gov/NationalFormulary.asp>). Consult VA pharmacists for alternatives.

Perform routine screening for STIs in all persons who are HIV-positive, since most STIs are asymptomatic.



EVALUATION

Providers should:

- Assess a patient's behavioral and biologic risks for acquiring or transmitting STIs and HIV (having sex without condoms, recent STIs, partners recently treated for STIs, multiple partners, use of agents that lower behavioral inhibitions such as alcohol).
- Assess a patient's oral, anal, vaginal sex behaviors to inform testing sites.
- Assess for symptoms: skin rash, urethral discharge, dysuria, ulcers in the genital, perineal, or perianal areas, regional lymphadenopathy, rectal discharge, pain on defecation or during anal intercourse, vaginal discharge.
- Offer regular screening.
- Screen for substance use as well given its impact on sexual risk behaviors.
- Test all sexually active persons with HIV infection for treatable STIs and perform testing at least annually during routine HIV care: serologic testing for syphilis, and screening for chlamydia and gonorrhea at exposed anatomic sites.
- Test MSM for HBsAg annually to detect chronic HBV infection and annually for hepatitis C.
- Immunize against HBV in at-risk individuals who have not been exposed to HBV.
- Screen women who are HIV-positive for *Trichomonas* at the initial visit and annually thereafter; screen for cervical cancer precursor lesions by cervical PAP tests per existing guidelines. The American Cancer Society recommends frequent PAP testing for women who are at high risk of cervical cancer because of a suppressed immune system.
- Offer treatment for STIs.
- Offer prevention counseling, including pre-exposure prophylaxis (PrEP) for partners who are HIV-negative.
- Report STIs to the local health department, including referrals to partner services programs.



SCREENING

Syphilis

- A positive nontreponemal tests: rapid plasma reagin (RPR) or Venereal Disease Research Laboratory (VDRL) or *T. pallidum* ELISA followed by a positive confirmatory treponemal test (MHA-TP, FTA-ABS or TP-PA) is the most common method. Some centers use a treponemal test as an initial screen and a nontreponemal test as a confirmatory test.

	<ul style="list-style-type: none"> • Neurosyphilis is diagnosed via clinical presentation and CSF examination. Cases of suspected neurosyphilis should be referred to Infectious Disease.
Chlamydia	<ul style="list-style-type: none"> • Urogenital infection: Nucleic acid amplification test (NAAT) on first-void urine (men and women); NAAT on vaginal or cervical swab (women). • Pharyngeal infection: Routine screening is not recommended because the prevalence of chlamydia pharyngeal infection is low. • Rectal infection: NAAT of rectal swab* (for all who report engaging in anal receptive sex)
Gonorrhea	<ul style="list-style-type: none"> • Urogenital infection: NAAT on first-void urine (men and women); NAAT on vaginal or cervical (women) or urethral (men) swab specimen; culture of male urethral or female endocervical swab specimen (in men, positive Gram stain of urethral specimen may be sufficient for diagnosis, a negative Gram stain does not rule out infection). • Pharyngeal infection: NAAT or culture of oral swab* (for all who report engaging in oral receptive sex). • Rectal infection: NAAT or culture of rectal swab* (for all who report engaging in anal receptive sex).
Trichomoniasis	Wet-mount examination or culture of vaginal secretions (for all women); NAAT urine (women) or penile meatal swabs (men) yearly testing in women who are HIV-positive.
HSV	HSV PCR or cell culture (persons with genital ulcers or other mucocutaneous lesions). HSV type- specific serologic testing for HIV-positive unaware of their HSV exposure.

Adapted from CDC. Sexually Transmitted Disease Treatment Guidelines—2015. See **References**.

Rx MANAGEMENT

Syphilis	<ul style="list-style-type: none"> • Primary, secondary and early latent syphilis: benzathine penicillin G 2.4 million units IM x1 dose (preferred), alternative therapy: doxycycline 100 mg po bid x14 days or ceftriaxone 1 g IM/IM or azithromycin 2 g po x1 *(azithromycin not recommended for MSM or pregnant women; the efficacy of non-penicillin alternatives has not been established in patients who are HIV-infected, close monitoring recommended). • Late latent syphilis (>1 year from known exposure, prior treatment or of unknown duration, CSF disease ruled out): benzathine penicillin G 2.4 million units IM weekly x3 dose (preferred) alternative therapy: doxycycline 100 mg po bid x28 days • Tertiary syphilis (cardiovascular or gummatous disease): benzathine penicillin G 2.4 million units IM weekly x 3 dose (preferred)
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	<ul style="list-style-type: none"> • Neurosyphilis (including otic and ocular disease): PCN G 3-4 million units IV q4 hours or 18-24 million units daily x 10 days by continuous infusion
Chlamydia	<ul style="list-style-type: none"> • Azithromycin 1 g po x1 or Doxycycline 100 mg bid x 7 days (preferred) • Consult Infectious Disease for alternative regimens
Gonorrhea	<ul style="list-style-type: none"> • Uncomplicated (treatment effective with single dose) - Ceftriaxone 250 mg IM x1 PLUS Azithromycin 1 g po x1 (preferred) • Cefixime 400 mg po x1 PLUS Azithromycin 1 g orally in a single dose
Trichomoniasis	<ul style="list-style-type: none"> • Metronidazole 500 mg po bid x 7 days in women who are HIV-positive
HSV	<ul style="list-style-type: none"> • Primary genital herpes: Acyclovir 400 mg po tid x 7–10 days or Valacyclovir 1 g orally bid x 7–10 days • Episodic treatment for recurrent genital herpes Acyclovir 400 mg po tid x 5-10 days or Valacyclovir 1 g po daily x 5 -10 days • Suppressive therapy: Valacyclovir 500 mg orally bid

See CDC STD Treatment guidelines for discussion.

Follow-up Testing

Test-of-cure to detect therapeutic failure in chlamydial infections (i.e., repeat testing 3–4 weeks post therapy) is not advised for persons treated with recommended or alternative regimens, unless therapeutic adherence is in question, symptoms persist, or reinfection is suspected.

Patients with persistent symptoms after treatment for gonorrhea and any patient with pharyngeal gonorrhea treated with an alternative regimen should return 14 days after treatment to be evaluated by culture for *N. gonorrhoeae* (with or without simultaneous NAAT). Any gonococcal isolate should be tested for antimicrobial susceptibility.

In syphilis, RPR titers are closely followed. RPR should be repeated at 3, 6, and 12 months after therapy—a significant change is a two dilution (or four fold) change in titer which represents a response to therapy.



WHEN TO REFER

- When neurosyphilis is suspected
- In patients with allergies to recommended regimens, for alternative regimens
- In case of treatment failure

Prevention

Adapted from cdc.gov:

- abstinence

- safer sexual practices - correct and consistent use of male or female condoms
- reduce number of sexual partners
- mutual monogamy
- vaccination (for human papilloma virus (HPV) and hepatitis B)



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HIV and Pain Management

Low Back Pain

KEY POINTS

- Low back pain (LBP) is a common complaint.
- Obtain a comprehensive history to determine etiology if LBP is pathologic or physiologic. The history will define the plan of care. LBP may be nonspecific and present with symptoms consistent with radiculopathy or spinal stenosis, evidence of systemic disease, or potentially be associated with another specific spinal origin. Assess for social or psychological distress that may contribute to chronic and/or disabling pain.
- Routine imaging or other diagnostic tests are not recommended for nonspecific LBP.
- **Red flag concerns that will require** diagnostic imaging and testing as follows: major trauma, age >50, unexplained fever, unexplained weight loss, injection drug use (IDU), immunosuppression, history of cancer, major muscle weakness, bladder or bowel dysfunction, unrelenting night pain, saddle anesthesia, decreased sphincter tone, focal neurologic deficit, duration >6 weeks, abdominal pulsating mass.
- Up to 90% of patients experiencing acute LBP without sciatica or systemic symptoms improve within 4 weeks.
- All patients with LBP should receive nonpharmacological interventions (e.g., heat/ice, creams, ointments, and movement-oriented therapies), nonsteroidal anti-inflammatory drugs (NSAIDs), or acetaminophen as indicated, and other interventions and medications as necessary. They also should be educated on the expected treatment course, and be advised to remain active.
- Follow up in 1-3 weeks and as needed. Reevaluate sooner in the event of worsening neurologic symptoms, bowel or bladder dysfunction, systemic symptoms, or failure to improve with initial management.



BACKGROUND

Epidemiology

Low back pain is described by some sources as “epidemic” and documented as the leading cause of disability globally, thus a major public health concern worldwide.

- Back pain is the second most common reason patients in the United States visit their physicians.
- In industrialized countries incidences of LBP is estimated at 70% over an individual’s lifetime.
- Approximately 15% to 45% of individuals experience LBP annually with 5% presenting to a hospital to obtain care.

Note: Some medications mentioned in this chapter may not be available on the VHA National Formulary (<https://www.pbm.va.gov/NationalFormulary.asp>). Consult VA pharmacists for alternatives.

- LBP is typically self-limiting to less than two weeks however:
 - 10% of those individuals may be unable to return to work;
 - 20% may continue to have persistent LBP symptoms at one year;
 - Less than 50% of those who have had complaint of LBP resulting in loss of work for six months will return to work; and
- Rate of return to work after two years of absenteeism is zero. Back pain can lead to chronic disability. Among patients who have had treatment for back pain, 72% have discontinued exercise and sports because of the pain, 60% have experienced limitations on their activities of daily living, and 46% have reported refraining from sexual activity.
- The physiologic cause of LBP cannot be definitively established in 85% of patients. Among such patients, LBP has been attributed to disc degeneration or muscular and ligamentous sources.
- Of patients who have LBP:
 - 70% have lumbar strains or sprains;
 - 10% have age-related degenerative processes of discs and facets;
 - 4% have herniated discs;
 - 3% have spinal stenosis;
 - 4% have osteoporotic compression fractures;
 - 1 - 3% have a prolapsed intervertebral disc;
 - 1% have a tumor;
 - <1% have urgent situations (red flags).

Definitions

Acute: Duration <4 weeks

Chronic: Duration >12 weeks

Sub-Acute: duration 4-12 weeks

Sciatica: Pain radiates past the knee along the sciatic nerve (posterior/lateral lower extremity)

Radiculopathy: Radiating pain, numbness, or muscle weakness that corresponds to impairment or impingement of a specific nerve root

Cauda equina syndrome: Urinary retention with overflow incontinence, saddle anesthesia, bilateral sciatica, and leg weakness. Usually caused by massive midline disc herniation or a tumor and represents a medical emergency

Spondylolisthesis: Slipping forward of one vertebral body over another. Patients may have back or leg pain; rarely, bladder or bowel symptoms or radicular pain

Spondylosis: Arthritis of the spine, with radiographically apparent disc space narrowing and arthritic changes at the facet joint. Associated with localized pain

or spasms with spinal flexion

Spinal stenosis: Local, segmental, or generalized narrowing of the central spinal canal by bone or soft tissue. Patients may experience *pseudoclaudication* or transient tingling in the legs, pain with walking, improvement with rest and with leaning forward, or with normal distal arterial pulses



EVALUATION

Check for red flags:

- Major trauma
- Age >50
- Duration >6 weeks
- Failure to improve with therapy
- Unexplained fever
- Unexplained weight loss
- Intravenous drug use (IVDU)
- CD4 count <200 cells/ μ L
- Transplant recipient
- Steroid use
- Bladder or bowel dysfunction
- Saddle anesthesia
- Decreased sphincter tone
- Focal neurologic deficit
- Diabetes
- History of cancer
- Major muscle weakness
- Unrelenting night pain
- Abdominal pulsating mass

Yellow Flags: Consider the biopsychosocial factors which may underline LBP such as (but not limited to) workers' compensation and disability claims, status of litigation, type and degree of social support, depression or other comorbid mental health disorder(s), socioeconomic status, substance abuse history, and availability of appropriate coping strategies.

In general, evaluate whether the patient has evidence of systemic disease, neurologic compromise, or social or psychological distress that may contribute to pain.

Use history and examination to place patients into 1 of 3 broad categories:

- Nonspecific LBP (about 85% of patients);
- Back pain potentially associated with radiculopathy or spinal stenosis (as suggested by the presence of sciatica and/or pseudoclaudication);
- Back pain potentially associated with another specific spinal cause; (see **Red Flags** below)
- Evaluate functional impact of LBP utilizing a self-report pain and disability questionnaire
 - e.g., the Oswestry Disability Index, which evaluates assessment items in 10 domains such as functional impact, personal care, and ability to manage activities of daily living.

Risk Factors	<ul style="list-style-type: none"> • Obesity • Older age • Female sex • Physically or psychologically strenuous work • Sedentary work • Job dissatisfaction (may affect return to work) • Smoking • Low educational attainment • Psychological factors: anxiety, depression, substance abuse
History	<ul style="list-style-type: none"> • Mechanism of onset, trauma • Location of symptoms, involvement of legs • Duration (acute <12 weeks, chronic >12 weeks) • Character of pain: mechanical, radicular, claudicatory • Limitations on activity • Neurologic symptoms: distribution, bowel or bladder symptoms, weakness, saddle anesthesia • Constitutional symptoms: fever, weight loss • Night pain • Previous spinal surgeries • Smoking history • Cancer • Corticosteroid use • Work-related injuries or repetitive stress • Psychological stressors, symptoms of anxiety, depression, substance abuse
Example History-taking Questions	<ul style="list-style-type: none"> • What are your symptoms? (ask about red-flag symptoms) • How do these symptoms affect you? How long can you sit, stand, etc.? What are you able to do/not able to do? • When did the current limitations begin? • How do you spend your time? (look for self-limiting behaviors and sedentary lifestyle) • What do you hope we can accomplish during this visit?
Physical Examination	<ul style="list-style-type: none"> • Observation of gait, position changes, and stance • Inspection of back and posture (scoliosis = lateral asymmetry; kyphosis = posterior convexity; lordosis = lumbar concavity)

	<ul style="list-style-type: none"> • Range of motion, including lumbar flexion (limited in ankylosing spondylosis) • Palpation of the spine (vertebral tenderness suggests fracture or infection) • Straight leg raising (SLR): sensitive but not specific for radiculopathy; pain with lifting leg of affected side (from lying position) from 10° to 60° • Cross-SLR: specific but not sensitive for radiculopathy; pain with lifting leg opposite affected side (from lying position) from 10° to 60° • Neurologic assessment of L4-S1 nerve roots: L4 injury corresponds to reduced unilateral knee extension strength and patellar reflex; L5 injury corresponds to numbness in the medial foot and web space between first and second toes; S1 injury corresponds to reduced unilateral ankle reflex, reduced sensation along the posterior calf and lateral foot; reduced ability to walk on tiptoes or heels for three steps • Evaluation for malignancy and infection if history and examination suggest a systemic disease (sites of interest include lymph nodes, prostate, breasts) • Check for Waddell's signs (e.g., nonorganic presentations of pain) • Inconsistent, incongruous, or contradictory physical signs in patients with chronic pain suggest psychological or social factors may also play a role in presentation
<p>Imaging</p>	<p>In the absence of red flag signs and symptoms, diagnostic studies such as plain films, Computerized Tomography (CT), or Magnetic Resonance Imaging (MRI)s are not indicated during initial evaluation of acute LBP nor will findings modify plan of care. Consideration in ordering such diagnostic imaging studies should be primarily driven by comprehensive history and physical examination.</p> <p>Imaging is indicated on presentation of symptoms in the patient with red-flag symptoms or any of the following symptoms for exam findings:</p> <ul style="list-style-type: none"> • Progressive neurological findings • Constitutional symptoms • History of traumatic onset • History of malignancy • Age ≤ 18 or ≥ 50 years

- Infection risk: IVDU, severe immunosuppression, prolonged corticosteroid use, skin or urinary tract infection, indwelling urinary catheter
- Suspected compression fracture (e.g., in persons with osteoporosis or prolonged steroid use)
- Plain film if LBP is the result of recent trauma to rule-out vertebral fracture.

If there is no clinical improvement after 6 weeks, obtain plain anteroposterior and lateral X rays of the lumbosacral spine to evaluate for tumor, infection, instability, spondyloarthropathy, or spondylolisthesis.

Computed tomography (CT) or magnetic resonance imaging (MRI) is indicated if there are progressive neurologic deficits or a high suspicion of cancer or infection, and should be considered for patients with >12 weeks of persistent LBP. In patients with persistent LBP and radiculopathy or signs of spinal stenosis, MRI (preferred) or CT is indicated if they are potential candidates for surgery or epidural steroid injection.

**Differential Diagnosis:
Red Flags for Specific Conditions and Suggested Initial Workup**

- **Cancer:** history of cancer, unexplained weight loss, age >50, pain >6 weeks, night pain
Evaluation: check CT or MRI of spine, check complete blood count (CBC) and erythrocyte sedimentation rate (ESR), and perform directed evaluation for suspected malignancy (e.g., prostate-specific antigen, mammogram, serum protein electrophoresis, urine protein electrophoresis)
- **Infection/osteomyelitis or Pott disease:** fever, IVDU, tuberculosis exposure risk, recent urinary tract infection, skin infection, pneumonia, corticosteroid use, transplant, diabetes, rest pain
Evaluation: MRI of the spine, CBC, ESR, urinalysis, blood and urine cultures
- **Cauda equina syndrome:** urinary retention or incontinence, saddle anesthesia, decreased anal sphincter tone, bilateral lower extremity weakness/numbness
Evaluation: immediate surgical consultation
- **Fracture:** corticosteroid use, age >70, osteoporosis, recent trauma
Evaluation: plain X-rays or CT, orthopedic consultation

- **Acute abdominal aneurysm:** pulsating abdominal mass, vascular disease, resting or night pain, age >60
Evaluation: ultrasound or CT to evaluate aorta, surgical consultation
- **Significant herniated nucleus pulposus:** major muscle weakness
Evaluation: MRI of the spine and surgical consultation

Rx MANAGEMENT

- Up to 90% of patients with LBP without sciatica or systemic symptoms have nonspecific LBP and improve within 4 weeks of starting conservative treatment.
- Recurrences are common, occurring in up to 40% of patients within 6 months after initial resolution.
- Goals of management are to reduce pain and disability using conservative measures, and to identify patients with more serious conditions that need further care.
- All patients with LBP should be prescribed nonpharmacological interventions and move up the analgesic and intervention “ladder” with extreme caution:
 - acetaminophen or NSAIDs +/- adjuvants →
 - weak opioids +/- adjuvants →
 - strong opioids +/- adjuvants
- Acetaminophen and NSAIDs are first-line medications for most LBP.
- **For chronic and subacute back pain, studies suggest that opiates show insufficient evidence of effectiveness to be recommended as treatment. Antiepileptic drugs, muscle relaxants, and benzodiazepines also demonstrate limited efficacy for managing chronic LBP.**
 - See VHA Pain Management Opioid Safety Initiative Toolkit for further information and details about appropriate use of opioids for management of chronic low back pain, https://www.va.gov/PAINMANAGEMENT/Opioid_Safety/index.asp.
 - Also helpful is the CDC Guideline for Prescribing Opioids for Chronic Pain.

Nonpharmacological Interventions

Intervention	Comments
<ul style="list-style-type: none"> • Patient education • Activity modification • Exercise • Physical therapy • Self-application of heat or cold to back • Manipulation • Other options available at specific VA sites (e.g., yoga, tai chi, MOVE!, etc.) <p>For Non-Radicular LBP - Moderate Strength of Evidence: Heat; exercise therapies (e.g., physical therapy, kinesiotherapy); psychological interventions (e.g., cognitive behavior therapy for chronic pain, relaxation training); acupuncture; multidisciplinary rehabilitation; low impact exercise.</p> <p>Cognitive behavior therapy provides pain education, expectation management, and a means for developing and employing various coping mechanisms to manage pain over time.</p> <p>For Radicular LBP - Low Strength of Evidence:</p> <p>Exercise; traction; spinal manipulation + home exercise + advice for radicular LBP.</p> <p>For Non-Radicular LBP - Low strength of evidence: massage; yoga; tai chi; motor control exercise; biofeedback; sham manipulation.</p>	<ul style="list-style-type: none"> • Patient education topics include appropriate expectations for recovery (e.g., acute vs. chronic), coping strategies and methods of symptom control, activity modifications, recognition of certain red-flag symptoms, and follow-up. • Clinical guidelines suggest first line care should include reassurance, importance of staying active, avoid bedrest. • Patients should be encouraged to walk and resume normal daily activities as soon as possible. • Avoid bedrest. Patients who go on longer bed rest have less improvement in pain and function than those who remain ambulatory. • Avoid prolonged periods of television viewing as this promotes sedentary lifestyle and prolonged sitting may have direct impact on lumbar spine. Television viewing should be limited to no more than 2 hours per day. • Activity modification should be minimal for acute back pain: Modifications might include limiting prolonged unsupported sitting, avoiding heavy lifting, and avoiding bending or twisting the back when lifting. • Maintain or start aerobic conditioning exercises, including swimming, walking, and stationary biking. • Avoid physical therapy for two weeks after onset of acute back pain. • Conduct workplace ergonomics evaluation if the back pain is related to work activities. • Chiropractic manipulation may be helpful in the first month of symptoms for selected patients who do not have radiculopathy or severe or progressive neurologic deficits. Refer to practitioners with specific training in manipulation (e.g., osteopathic physicians).

Pharmacologic

For dosages and additional information, see **Pain Medications**, p. 31.

The medications listed below may be utilized for the treatment of LBP. Providers have a responsibility to educate their patients that review of the literature reveals most pharmacological options have a small-to-moderate, and short term effect on pain. This obligates the provider and patient to seek pragmatic management past the acute phase that may include a transdisciplinary approach to ensure the best physical and psychosocial outcomes to decrease the potential for medication overuse; thus preventing adverse events.

Intervention	Comments
<p>Acetaminophen Low Strength of Evidence</p>	<ul style="list-style-type: none"> • First-line analgesic because of its safety profile. • Use for patients who cannot tolerate NSAIDs. • Possible adverse effects include hepatotoxicity (especially if taken with alcohol) and nephrotoxicity (with chronic overdose).
<p>NSAIDs</p> <ul style="list-style-type: none"> • Ibuprofen • Naproxen • Sulindac • Ketorolac IM • Celecoxib <p>Radicular LBP: Low Strength of Evidence Non-radicular Acute or Subacute LBP: Moderate Strength of Evidence</p> <p>May trial another NSAID if first is not effective as no one NSAID is noted to be superior.</p>	<ul style="list-style-type: none"> • First-line analgesic. • May not confer additive benefit when used with high-dose acetaminophen. • Avoid use for patients with peptic ulcer disease or cirrhosis. • Monitor for nephrotoxicity. • May increase risk of cardiovascular events: rofecoxib (COX-2 inhibitor) was withdrawn from the market owing to observational data showing greater risk than celecoxib; diclofenac confers greater risk than other nonselective NSAIDs.
<p>Tricyclic antidepressants (TCAs) and Serotonin and norepinephrine reuptake inhibitors (SNIRs) (e.g., amitriptyline, nortriptyline, duloxetine)</p> <p>Efficacy is still being studied. Mechanisms of action are still being determined (e.g., if pain improves because co-occurring depression also improves). Duloxetine is noted to have a Moderate Strength of Evidence for the treatment of LBP.</p>	<ul style="list-style-type: none"> • Consider for neuropathic pain; also consider as an adjunct for any type of LBP unresponsive to acetaminophen and NSAIDs. • Anticholinergic and other adverse effects, especially at higher doses.

Intervention	Comments
<p>Muscle relaxants (nonbenzodiazepines)</p> <ul style="list-style-type: none"> • Cyclobenzaprine • Baclofen • Tizanidine • Metaxalone <p>Moderate evidence exists above medications may be effective for short term use (7-14 days) of acute LBP and in conjunction with NSAIDs efficacy may be enhanced.</p> <p>Low quality evidence indicates efficacy diazepam and carisoprodol (Soma) may be used briefly (five days) due to incidence of abuse and dependence.</p>	<ul style="list-style-type: none"> • May be useful as adjunctive therapy for acute back pain but not recommended for chronic or subacute back pain. • Short-term (1-3 week) use.
<p>Anticonvulsants</p> <p>Topiramate</p>	<ul style="list-style-type: none"> • May be more effective than placebo for short-term chronic LBP.
<p>Benzodiazepines</p>	<ul style="list-style-type: none"> • May be useful as adjunctive therapy for acute back pain but not recommended for chronic or subacute back pain. • Second-line muscle relaxant after cyclobenzaprine or baclofen. • No data is available comparing the relative efficacy and safety of the various benzodiazepines. • A time-limited course (1-3 weeks) is recommended, owing to the risk of abuse, addiction, and tolerance.
<p>Epidural steroid injections (ESIs)</p> <p>Medications may include corticosteroids, lidocaine, and opioids.</p> <p>ESIs are not considered more effective than placebo for long term relief of chronic LBP and addition of lidocaine was no better than placebo.</p>	<ul style="list-style-type: none"> • For short-term relief of radicular pain; consider after failure of conservative treatment. • Epidural steroid injections have not been shown to reduce the rates of subsequent disc surgery. • Refer to back pain specialist or orthopedist.
<p>Systemic corticosteroids: Moderate Strength of Evidence</p>	<p>-</p>
<p>Opiate analgesics</p> <p>No rigorous evidence supports opioid use for acute or chronic LBP and the lack of data associated with the efficacy should be weighed assuming the associated risks</p>	<ul style="list-style-type: none"> • Consider opioids for patients who have severe pain refractory to the interventions listed above (nonpharmacologic and pharmacologic) or cannot receive those therapies.

Intervention	Comments
<p>of opioid use. Options include:</p> <ul style="list-style-type: none"> • Tramadol (not a typical opiate; exact mechanism of action is unknown; acts in part as a central opioid agonist) <p>Weak opioids</p> <ul style="list-style-type: none"> • Codeine • Hydrocodone + acetaminophen • Oxycodone + acetaminophen <p>Strong opioids</p> <ul style="list-style-type: none"> • Morphine • Oxycodone • Hydromorphone • Fentanyl transdermal 	<ul style="list-style-type: none"> • For very short-term use in severe acute exacerbations, and for severely disabling chronic back pain: start with weak opioids; assess safety, efficacy, and usage; titrate up or continue prescription only if evidence for functional improvement is clear. • Use the lowest effective dosage. • If needed for acute flares, limit use to a designated short period of time. • If needed for chronic pain, try to use a sustained release opioid with scheduled dosing around the clock, with shorter-acting opioids for breakthrough pain as needed. • Risk of dependence, overdose: monitor closely. • Adverse effects include oversedation, hypotension, respiratory depression, central nervous system stimulation or somnolence, dizziness, constipation, nausea, and pruritus. • Note that tramadol 37.5 mg + acetaminophen 325 mg has shown pain relief equivalent to codeine 30 mg + acetaminophen 325 mg but with fewer side effects (major side effect: headache). • Chronic opioid therapy should incorporate an opioid use agreement that includes functional goals for outcome, not reduced pain intensity alone.



WHEN TO REFER

Refer emergently to Neurosurgery or Orthopedic Surgery for:

- Cauda equina syndrome
- Spinal cord compression
- Progressive or severe neurologic deficit

Consider referral to Neurosurgery or Orthopedic Surgery for patients with persistent LBP or sciatica caused by:

- Disc herniation

- Spinal stenosis
- Spondylolisthesis

Consider referral to Physiatry for patients who are not improving:

- Chronic back pain >12 weeks
- Chronic sciatica <4-6 weeks
- Chronic pain syndrome
- Recurrent back pain

Consider referral to Neurology for:

- Chronic sciatica >6 weeks
- Atypical chronic leg pain (negative SLR)
- New or progressive neuromotor deficit

Consider referral to Rheumatology for patients with persistent symptoms to:

- Rule out inflammatory arthropathy
- Rule out fibrositis/fibromyalgia (e.g., LBP plus widespread pain complaints)
- Rule out metabolic bone disease (e.g., osteoporosis)

Prevention

- Conduct ergonomic evaluation of work areas and implement ergonomic design of job tasks.
- Exercise has shown benefit in preventing first episodes of back pain, preventing recurrences after episodes of back pain (initiate exercise after episode is complete), and reducing the perception of back pain.

Follow-Up

- Follow up in 1-4 weeks with a phone call or visit and as needed. Follow-up is necessary when there is worsening of neurologic symptoms, bowel or bladder dysfunction, presence of systemic symptoms, or failure to improve with initial management.



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Peripheral Neuropathy

KEY POINTS

- HIV-associated peripheral sensory neuropathy (HIV-SN) commonly includes distal sensory polyneuropathy (DSP) and ARV toxic neuropathy.
- Patients typically present with bilateral tingling, numbness, or neuropathic pain starting in their toes and spreading proximally; the pain frequently is described as burning or aching and is worse on the soles.
- Peripheral neuropathy is more common in particular racial/ethnic groups, older individuals, age, the presence of comorbidities such as diabetes, hypertension and specific genetic factors; management should include optimizing treatment of chronic diseases such as diabetes that increase the risk or severity of peripheral neuropathy.
- Patients frequently have impaired sensation and vibratory sense without pain.
- The ACTG Peripheral Neuropathy Screening Tool (available in this chapter) is a simple evaluation instrument that takes less than five minutes to complete. Ask about distal numbness and check ankle reflexes. Screening for numbness and delayed or absent ankle reflexes has the highest sensitivity and specificity among the clinical evaluation tools.
- Treat suspected ARV toxic neuropathy by withdrawing the offending drug, if possible.
- Treat the pain of HIV-SN with analgesics, anticonvulsants, and topical medication; if severe, and as a last resort, treat with long-acting narcotics.



BACKGROUND

- HIV-SN is a “dying-back” or “stocking-glove” peripheral neuropathy, initially affecting the most distal fibers and involving myelinated and unmyelinated axons. On pathologic examination, this pattern of loss is indistinguishable from other toxic neuropathies.
- Patients typically present with bilateral tingling, numbness, or neuropathic pain that starts in the toes and spreads proximally; the pain frequently is described as burning or aching and is worse on the soles. It also may be described as shock like or knifelike.
- HIV-SN includes:
 - DSP caused by HIV infection itself.
 - ARV toxic neuropathy resulting from exposure to ARVs, particularly d4T, ddI, and ddC (the “dNRTIs” or “d-drugs”). The onset can occur as early as 9 weeks after starting the offending agent.
- DSP is thought to be related to chronic immune activation, leading to macrophage overproduction of proinflammatory cytokines and chemokines in the peripheral nervous system.

Note: Some medications mentioned in this chapter may not be available on the VHA National Formulary (<https://www.pbm.va.gov/NationalFormulary.asp>). Consult VA pharmacists for alternatives.

- ARV toxic neuropathy is thought to be associated with mitochondrial toxicities of the dNRTIs.
- Many other drugs and conditions may cause peripheral neuropathy (PN) or compound the condition. It is not uncommon for patients to have reason(s) for neuropathy other than their HIV (e.g., comorbid diabetes and HIV).

Epidemiology

- In the Goulee 2016 study, HIV-associated sensory neuropathy was found to be the most common neurological condition associated with HIV, affecting up to 50% of HIV individuals.
- A recent study by Smyth showed the prevalence of HIV-SN was 42% among patients at an outpatient clinic in Australia; 92% of patients with sensory neuropathy were on ARVs.
- In a predominately female HIV-1 population (69.8%) in Cameroon the prevalence of HIV-SN was 96.9%. In this outpatient clinic 83.9% of patients were diagnosed with sensory neuropathy prior to initiating highly active antiretroviral therapy (HAART) while 16.3% developed symptoms while on HAART (Luma).
- In a cohort of treatment-naïve patients, 22.6% had PN without pain whereas 4.6% had symptomatic painful neuropathy; in the majority, PN persisted despite effective control of HIV with ARV therapy (Evans).
- The risk of developing PN is higher for patients with **advanced** HIV infection (Evans).
- The annual incidence of DSP among patients with CD4 counts of <200 cells/ μ L is 7%. In two studies from the 1980s, 30% of patients hospitalized with advanced AIDS had DSP in the absence of ARV therapy (McArthur).
- Although a risk factor, as discussed above, Smyth cites studies that suggest that in the post-cART-era, neither CD4 count nor viral load correlate with the incidence of PN.

Prevention

Prevention and early intervention are vitally important in avoiding or reversing symptoms of neuropathy.

- Give ARV therapy according to usual guidelines to avoid increased risk of HIV-SN resulting from advanced HIV disease.
- Avoid ARVs (particularly d4T and ddI) associated with neurotoxicity.
- If possible, avoid non-ARV medications that may cause PN.
- Avoid treatment regimens that have additive neurotoxicity (e.g., metronidazole for a patient who is receiving isoniazid).

- With patients who develop ARV toxic neuropathy, discontinue the causative ARV if a reasonable substitution can be made.
- Maximize medical management of all comorbid chronic diagnoses such as but not limited to diabetes, hypertension, hyperlipidemia, vascular disease, and alcoholism.



EVALUATION

DSP and ARV toxic neuropathy are clinically indistinguishable, although the timing of symptom onset may help to differentiate the etiology.

Risk factors	<ul style="list-style-type: none"> • Increasing age, height • Exposure to d4T, ddl, or ddC • Advanced untreated HIV (low CD4 count nadir, high HIV RNA) • Alcohol use • Nutritional deficiencies (e.g., vitamin B12) • Other neurotoxic medications, e.g.: 	
	Dapsone Hydroxyurea Metronidazole Vincristine	Thalidomide Isoniazid Linezolid Ribavirin
	<ul style="list-style-type: none"> • Diabetes, impaired glucose tolerance 	



SCREENING

Quick Screen

Ask about distal numbness and check ankle reflexes.

- Use the **ACTG Peripheral Neuropathy Screening Tool** (see below). This is a validated screening tool for scaling the degree of PN. It includes subjective and objective information, and takes <10 minutes to administer.
- HIV-SN can be diagnosed when a patient exhibits **≥1 symptom specified in the ACTG Peripheral Neuropathy Screening Tool and one of the following: diminished ankle reflexes, reduced vibration sense at the first toe.**
- Serial assessment of ACTG Peripheral Neuropathy Screening Tool scores allows tracking of symptom severity and response to treatment.

<p>History</p>	<ul style="list-style-type: none"> • Ask about numbness, pain, location/distribution of symptoms, character or quality of pain, other neurologic symptoms, duration, exposure to dNRTIs and other neurotoxic drugs. • Numbness has a sensitivity of 86% and a specificity of 81% for the clinical diagnosis of HIV-SN. Asking about numbness has greater sensitivity for the diagnosis of HIV-SN than asking about pain.
<p>Physical Examination</p>	<p>Perform a thorough neurologic examination. Characteristics of HIV-SN:</p> <ul style="list-style-type: none"> • Reduced or absent ankle Achilles tendon reflexes; this has a sensitivity of 84% and a specificity of 98% for HIV-SN. • Distal sensory loss (temporal progression: loss of vibratory sense occurs first, followed by loss of temperature sensation, followed by pain). • Findings usually are bilateral and symmetric.
<p>Differential Diagnosis</p>	<ul style="list-style-type: none"> • Toxicity (e.g., alcohol, B6) • Non-ARV medication toxicity • Nutritional deficiency (e.g., vitamin B12) • Folic acid deficiency • Diabetes, impaired glucose tolerance • Hypothyroidism • Other HIV-associated neuropathies, including: <ul style="list-style-type: none"> • Inflammatory demyelinating polyradiculoneuropathy • Cauda equina syndrome • Neuromuscular weakness syndrome • Diffuse infiltrative lymphocytosis syndrome (DILS) • Autonomic neuropathy • Mononeuritis • Polyradiculitis • Cryoglobulinemia (especially in hepatitis C virus-infected patients) • Syphilis • Herpes zoster radiculitis • Plantar fasciitis, musculoskeletal conditions, tarsal or carpal tunnel compression <p>Note: <i>Patients with foot pain or numbness may have ≥1 source of symptoms.</i></p>

<p>Findings that Suggest a Different Diagnosis</p>	<ul style="list-style-type: none"> • Prominent weakness (consider inflammatory demyelinating polyneuropathies, HIV-associated neuromuscular weakness syndrome, especially with d4T use – check lactic acid levels) • Neuropathy in the hands more so than in the feet (consider carpal tunnel syndrome) • Proximal features (consider inflammatory demyelinating polyneuropathies) • Marked asymmetry (consider mononeuritis multiplex, especially with foot drop) • Sphincter dysfunction (consider progressive polyradiculoneuropathy, especially caused by cytomegalovirus) • Cranial nerve involvement (consider progressive polyradiculoneuropathy) • Tenderness or deformity in plantar foot or joints (consider plantar fasciitis, gout)
<p>Laboratory Evaluation</p>	<p>Screen for:</p> <ul style="list-style-type: none"> • Diabetes (fasting glucose; consider HbA1c) • Vitamin B12 deficiency (check B12 level; if low, check RBC folate, methylmalonic acid levels, and intrinsic factor antibody titers) • Hypothyroidism (TSH, T4) • Syphilis (RPR or VDRL) • Renal failure (serum creatinine, blood urea nitrogen; consider serum protein electrophoresis) • Hepatitis C (HCV IgG/PCR) • Monoclonal gammopathies (serum protein electrophoresis) • If patient is taking supplements/energy drinks, consider checking B6 level
<p>Further Evaluation</p>	<ul style="list-style-type: none"> • Electromyography and nerve conduction velocity studies are not needed unless the symptoms are complex or there are atypical findings, or concern for focal compression neuropathy, such as carpal tunnel syndrome. • Sensory threshold testing is used primarily in research settings. • Punch biopsy for pathologic evaluation of epidermal nerve density may be useful in differentiating HIV-SN and other causes. • Consider referral of patients to neurologist or podiatrist if the diagnosis is unclear.

Rx MANAGEMENT

- Goals: relieve pain, halt progression of symptoms.
- Patients taking neurotoxic medications: discontinue these if possible.
- Patients not on ARV therapy: consider initiation.
- Pharmacologic treatment often is multimodal, involving several types of medications.
- Consider starting with an anticonvulsant such as gabapentin or pregabalin and titrating to effect.
- Add or use antidepressants: selective serotonin-norepinephrine reuptake inhibitors (SNRIs) (duloxetine or venlafaxine) may improve neuropathy pain, especially for patients with comorbid depression; tricyclic antidepressants (TCAs) are of limited benefit, and anti-cholinergic toxicities may limit their tolerability.
- Add or use topical agents (capsaicin or lidocaine (cream or patch)) for patients who need additional pain control or cannot tolerate systemic pain medications.
- Do a trial of NSAIDs or acetaminophen; these are useful for some PN patients.
- For severe or recalcitrant symptoms, consider as an absolute last resort adding a long-acting opioid.



WHEN TO REFER

Refer to a pain specialist or neurologist if symptoms are not controlled with initial trials of medication.

Pharmacologic

Intervention	Medications	Comments
Discontinuation of offending drug (e.g., switching from dNRTIs, avoiding combinations with additive neurotoxicity)	Not applicable	<ul style="list-style-type: none">• Differentiate DSP and ARV toxic neuropathy by timing of symptom onset.• Prompt discontinuation of a neurotoxic medication may prevent progression of symptoms, and may allow reversal of symptoms.

		<ul style="list-style-type: none"> • Before discontinuing an offending drug, carefully weigh risks and potential benefits. • Consider dosage reduction of d4T, if discontinuation is not possible. • With ARV toxic neuropathy caused by a dNRTI, symptoms often improve within 3 months (though they may be permanent).
Initiation of ARV Therapy	<ul style="list-style-type: none"> • Avoid dNRTIs 	<ul style="list-style-type: none"> • Initiation of ARV therapy can improve non-ARV-associated DSP for patients with advanced HIV who have uncontrolled viremia and low CD4 counts.

Medications

For dosages and additional information, see **Pain Medications**, p. 31.

Mild Analgesics	<ul style="list-style-type: none"> • Acetaminophen • NSAIDs 	<ul style="list-style-type: none"> • Use as first-line therapy for mild symptoms. • Can use in combination with tricyclic antidepressants (TCAs), anticonvulsants, and topical adjuncts. • Avoid use or limit dosages for patients with underlying liver or renal disease.
Anticonvulsants	<ul style="list-style-type: none"> • Gabapentin • Pregabalin • Lamotrigine 	<ul style="list-style-type: none"> • Gabapentin: considered first-line for its tolerability. • Pregabalin: sometimes better tolerated than gabapentin. Little evidence of efficacy for HIV-SN (*not superior nor more effective than placebo). • Lamotrigine: has shown the greatest efficacy in clinical trials for HIV-SN. • Data for other anticonvulsants, such as topiramate, are lacking. Topiramate may be useful for selected patients with close monitoring. • To discontinue these agents, taper slowly over course of ≥ 7 days. <p>Potential ARV Interactions</p> <ul style="list-style-type: none"> • Lopinavir/ritonavir and atazanovir/

		ritonavir both resulted in decreased bioavailability of lamotrigine.
Antidepressants; TCAs and SNRIs	<ul style="list-style-type: none"> • TCAs: amitriptyline and nortriptyline • SNRIs: venlafaxine and duloxetine; these are inadequately studied in patients with HIV infection 	<ul style="list-style-type: none"> • Consider SNRIs for patients with comorbid depression. • Small studies have shown limited or negative results with TCAs. • TCAs may cause sedation. • Monitor serum TCA levels and EKG to avoid cardiotoxicity at higher dosage levels. <p>Potential ARV Interactions</p> <ul style="list-style-type: none"> • Drug interactions: RTV and other PIs may increase the level of TCAs; start at low dosage, increase slowly.
Topical Anesthetics	<ul style="list-style-type: none"> • Capsaicin patch or cream • Lidocaine patch 	<ul style="list-style-type: none"> • A single capsaicin patch application can provide some degree of pain relief for up to 12 weeks. • Topical lidocaine has not shown significant benefit over placebo, and is expensive. Consider brief trial for patients with incomplete pain relief on other therapies.
<p>Opiate Analgesics</p> <p>**Need to consult and follow CDC recommendations and VA policy regarding dispensing of opiates.</p>	<p>Long-acting narcotics preferred:</p> <ul style="list-style-type: none"> • Transdermal fentanyl • Long-acting morphine • Methadone • Long-acting oxycodone 	<ul style="list-style-type: none"> • For moderate to severe HIV-SN with an inadequate response to the therapies listed above. • Titrate carefully. For more information, see Pain Medications, p. 31. • Methadone: acts on NMDA receptors; may give adjunctive benefit. Caution: start at low dosage and titrate slowly because of its long half-life; consult with pharmacist. • Transdermal fentanyl is appropriate only for patients already on stable dosage of other opiates: start at equianalgesic (or lower) dosage. <p>Potential ARV Interactions</p> <ul style="list-style-type: none"> • Ritonavir and Fentanyl – increased sedation, confusion, respiratory depression • Decreased methadone effects

ACTG Peripheral Neuropathy Screening Tool

Instructions for Recording Subjective Elicited Symptoms

Ask the subject to rate the severity of each symptom listed in Question 1 on a scale of 01 (mild) to 10 (most severe) for right and left feet and legs. Enter the score for each symptom in the columns marked R (right lower limb) and L (left lower limb). If a symptom has been present in the past, but not since the last visit, enter “00 – Currently Absent.” If the symptom has never been present, enter “11 – Always Been Normal.”

Always Been Normal	Currently Absent	Mild ←————→ Severe									
		11	00	01	02	03	04	05	06	07	08

1. Symptoms

- Pain, aching, or burning in feet, legs
- “Pins and needles” in feet, legs
- Numbness (lack of feeling) in feet, legs

R	L
-	-
-	-
-	-

Instructions for Grading Subjective Elicited Symptoms

Use the single highest severity score from Question 1 above to obtain a subjective sensory neuropathy score. If all severity scores are “00” or “11,” the subjective sensory neuropathy score will equal “0.”

Presence/Severity Score of:

01 – 03 = grade of 1

04 – 06 = grade of 2

07 – 10 = grade of 3

11 or 00 = grade of 0

2. Subjective Sensory Neuropathy Grade

R	L
-	-

3. Location of symptoms

Use Score of:

0 = none

1 = feet only

2 = extends to ankles

3 = extends above ankle but not to knee

4 = extends to knees

5 = extends to knees

R	L
-	-
-	-
-	-

- Pain, aching, or burning in feet, legs

b. “Pins and needles” in feet, legs

c. Numbness (lack of feeling) in feet, legs

Instructions for Evaluation Perception of Vibration

Compress the ends of a 128-Hz tuning fork just hard enough that the sides touch. Place the vibrating tuning fork on a bony prominence on the subject’s wrist or hand to be sure that he/she can recognize the vibration or “buzzing” quality of the tuning fork. Again, compress the ends of the tuning fork just hard enough that the sides touch. Immediately place the vibrating tuning fork gently but firmly on the top of the distal interphalangeal (DIP) joint of one great toe and begin counting the seconds. Instruct the subject to tell you when the “buzzing” stops. Repeat for the other great toe.

4. Vibration Perception

a. Great toe DIP joint perception of vibration in seconds

b. Vibration perception score

R	L
-	-

Vibration Perception

- 0 = felt >10 seconds (normal)
- 1 = felt 6-10 seconds (mild loss)
- 2 = felt <5 seconds (moderate loss)
- 3 = not felt (severe loss)
- 8 = unable to or did not assess

Instructions for Evaluating Deep Tendon Reflexes

With the subject seated, the examiner uses one hand to press upward on the ball of the foot, dorsiflexing the subject’s ankle to 90 degrees. Using a reflex hammer, the examiner then strikes the Achilles tendon. The tendon reflex is felt by the examiner’s hand as a plantar flexion of the foot, appearing after a slight delay from the time the Achilles tendon is struck. Use reinforcement by having the subject clench his/her fist before classifying the reflex as absent.

Ankle Reflexes

- 0 = absent
- 1 = hypoactive
- 2 = normal deep tendon reflexes
- 3 = hyperactive
- 4 = clonus
- 8 = unable to or did not assess

R	L
-	-

5. Ankle Reflexes



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Chronic Pain in HIV – General Management

KEY POINTS

- Chronic pain is a common and significant problem in people with HIV.
- Pain in patients with HIV is underestimated and undertreated, hence screening for pain in a systematic fashion is recommended.
- Assess chronic pain in patients who are HIV-positive in the same manner as in patients who are HIV-negative.
- First line of therapy consists of non-pharmaceutical measures and non-opioid analgesics.
- Opioid analgesics should be prescribed with caution in accordance with current guidelines and after careful risk assessment.



BACKGROUND

Patients with HIV have an increased rate of chronic pain, particularly peripheral neuropathy. Ongoing pain is present in 39-85% of patients with HIV. Chronic pain causes significant disability and negatively affects quality of life.

HIV related pain may be neuropathic or non-neuropathic. See **Table** below.

Pain management must take multiple factors into account (complex ARV (antiretroviral) drug regimens, higher risks of side effects, comorbid medical disorders, higher rates of comorbid psychiatric illness and substance abuse), and use all available modalities, including non-opioid pain relievers, adjuvant medications, and psychosocial therapies in addition to opioid analgesics. In studies, opioids did not demonstrate significant improvement in physical or emotional functioning.

Having the pain appropriately managed, with the goal of restoring function and improve quality of life is a basic human right. Understanding patients' chronic pain experience from a psychosocial, in addition to a biological, perspective is a critical first step toward improving care for this population.

Patients with HIV should be assessed for chronic pain and offered pain management options. The goal of treatment is to restore function.

The guidelines recommend offering alternative, non-pharmacological therapies first. If medication is needed, the guidelines recommend beginning with non-opioid medications.

Types of Pain in HIV

- Half of the pain is neuropathic (related to HIV itself or side effect of HIV drugs-rarely seen with modern ARV therapy). Other causes are alcohol use, syphilis, INH (isoniazid) treatment, vitamin deficiencies, thyroid dys-

Note: Some medications mentioned in this chapter may not be available on the VHA National Formulary (<https://www.pbm.va.gov/NationalFormulary.asp>). Consult VA pharmacists for alternatives.

function, multiple myeloma and diabetes. Distal sensory PN (peripheral neuropathy) can cause feelings of numbness, tingling, burning, itching, electrical, or shooting pain (See **Peripheral Neuropathy**, p. 543).

- Non-neuropathic pain is caused by inflammation, infection or neoplasia. Most common cause of non-neuropathic pain is musculoskeletal (OA and nonspecific LBP (low back pain)).



EVALUATION

Screening questions:

- How much bodily pain have you had during the week?
- Do you have bodily pain that has lasted more than 3 months?

Chronic pain is defined as any pain that lasts for 3 to 6 months or more. If the screening for pain is positive, provider should:

- Take a thorough history: severity of pain, location/distribution of symptoms, character or quality of pain (including pain descriptors and constant/intermittent nature of pain), predisposing and alleviating factors, numbness and other neurologic symptoms, duration, determination of how pain impacts function (ADLs/IADLs, mobility, sleep, work and avocational activities) and quality of life, and exposure to ARV therapy and to neurotoxic drugs.
- Perform a physical exam (absence of ankle Achilles tendon reflexes, stocking distribution sensory changes, hyperalgesia, and allodynia suggest PN).
- Perform a psychosocial evaluation.
- Screen for depression (PHQ-2) and neurocognitive disorder.
- Perform diagnostic testing tailored to patient symptoms.
- Make a treatment plan.
- Periodically assess the response to treatment.
- Communicate in an empathetic and supportive manner.

Assessment

- Assess for chronic pain in patients who are HIV-positive.
- Assess for common mental health disorders and unhealthy substance use.
- Assess any new pain in patients who have controlled chronic pain.

For the complete reference of medications indications and dosages, see **Pain Medications: Dosage and Indications**, p. 31.

Type of pain	Therapeutic Modalities	Description
Chronic pain (neuropathic and non-neuropathic)	Non-pharmacologic	<ul style="list-style-type: none"> • CBT (cognitive behavioral therapy) • Yoga • Tai Chi • PT/OT • hypnosis • acupuncture • shoe orthotics and assistive devices (e.g., bed cradles)
Chronic neuropathic pain	Pharmacologic	<ul style="list-style-type: none"> • early initiation of ARV therapy • first line: gabapentin (up to 2400mg/day in divided doses) • if inadequate response to gabapentin or adverse drug effect: <ul style="list-style-type: none"> • SNRIs (serotonin-norepinephrine reuptake inhibitors) (sustained-release venflaxine, duloxetine) • TCA (tricyclic antidepressants) (amitriptyline, nortriptyline, desipramine) • pregabalin (in PHN (postherpetic neuralgia)) • capsaicin topical 8% patch or cream • medical cannabis (in appropriate patients) • alpha-lipoic acid (600mg daily) • second and third line: time limited trial of opioids
Chronic non-neuropathic pain	Pharmacologic	<ul style="list-style-type: none"> • first line: acetaminophen (max 4g/day, lower maximum dose, of 2g/day in patient with comorbid liver disease) and NSAIDs (with attention to GI (gastrointestinal) side effects) • tramadol (in OA (osteoarthritis)), maximum 400 mg/day • second and third line: time limited trial of opioids

If using a trial of chronic opioid treatment, providers should:

- Discuss the potential risks and benefits of opioids use.
- Assess the risk of developing negative consequences (misuse, diversion, addiction) on opioids.
- Routinely monitor patients (monthly for high risk patients (e.g. those with recent history of substance use)).
- Have an opioid patient-provider agreement (that includes consent and plan of care).
- Start the smallest effective dose and combine short-acting opioids (e.g. hydrocodone-acetaminophen) with long-acting opioids (e.g. morphine sulfate controlled-release).
- Understand the clinical use and limits of urine drug screen (UDS) (baseline UDS prior to initiation, then every 1-3 month for adherence monitoring, and random UDS for unexpected results or concerning behavior patterns). **Note: unexpected UDS results should not be used in isolation to discharge patients from care.**
- Evaluate patients with history of substance use disorder or addiction in the same manner as other patients with chronic pain.
- Screen for cognitive impairment.
- Consult with pharmacist in patients who are on methadone or buprenorphine for treatment of opioid use disorder.
- Use appropriate techniques when continuation of controlled substances is not indicated or no longer useful.



WHEN TO REFER

HIV providers must work closely with pain specialists, psychiatrists and physical therapists to help alleviate their patients' pain.

Refer to pain specialists when a patient needs an opiate dosage that exceeds the expected duration and amount.

Refer to MH (mental health) for management if comorbid psychiatric conditions, when unhealthy substance use is present, or if aberrant behavior develops while on opiates.

Refer to palliative care specialist in patients with HIV with chronic pain at the end of life.



POTENTIAL ARV INTERACTIONS

- NNRTIs (nonnucleoside inhibitors) (e.g. efavirenz) significantly reduce methadone concentration, increasing risk of opiate withdrawal.
- Ritonavir increases level of oxycodone.
- AZT toxicity might be increased in combination with opioids (monitor) and dose reduction might be required in patients on methadone.



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